Introduction

The bone marrow is filled with cells known as hematopoietic stem cells. These immature cells develop into different types of blood cells: white blood cells to fight infection, red blood cells to carry oxygen, and platelets to clot the blood. In some cases, treating cancer also means destroying the bone marrow’s natural ability to create healthy blood cells. Restoring this function means returning these immature cells — the hematopoietic stem cells — to the body. When the immature blood cells come from a donor it’s known as an allogeneic transplant. When the cells are collected from the patient, stored, and later given back to the same patient it’s called an autologous transplant (autologous means from the same person). This policy describes when these transplants may be considered medically necessary for acute myeloid leukemia.

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.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Allogeneic hematopoietic cell transplantation (HCT)** | Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen may be considered medically necessary to treat:  
  - Poor- to intermediate-risk acute myeloid leukemia (AML) in first complete remission (CR1) (see Table 1)  
  OR  
  - AML that is refractory to standard induction chemotherapy but can be brought into CR with intensified induction chemotherapy  
  OR  
  - AML that relapses following chemotherapy-induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy  
  OR  
  - AML in patients who have relapsed following a prior autologous HCT, but can be brought into CR with intensified induction chemotherapy and are medically able to tolerate the procedure                                                                                                                                 |
| **Allogeneic HCT using a reduced-intensity conditioning regimen** | Allogeneic HCT using a reduced-intensity conditioning regimen may be considered medically necessary as a treatment of AML in patients who are in complete marrow and extramedullary remission (CR1 or beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.                                                                                                           |
| **Autologous HCT**                              | Autologous HCT may be considered medically necessary to treat AML in CR1 or beyond, or relapsed AML, if responsive to intensified induction chemotherapy in patients who are not candidates for allogeneic HCT.                                                                                                                                                |
Primary refractory acute myeloid leukemia (AML) is defined as leukemia that does not achieve a complete remission after conventionally dosed (non-marrow ablative) chemotherapy.

In the French-American-British criteria, the classification of AML is solely based on morphology as determined by the degree of differentiation along different cell lines and the extent of cell maturation.

Clinical features that predict poor outcomes of AML therapy include, but are not limited to, the following:

- Treatment-related AML (secondary to prior chemotherapy and/or radiotherapy for another malignancy)
- AML with antecedent hematologic disease (eg, myelodysplasia)
- Presence of circulating blasts at the time of diagnosis
- Difficulty in obtaining first complete remission with standard chemotherapy
- Leukemias with monocytoid differentiation (French-American-British classification M4 or M5)

The newer, currently preferred, World Health Organization (WHO) classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers. It attempts to construct a classification that is universally applicable and prognostically valid. The WHO system was adapted by National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management, as shown in Table 1.

### Table 1. Risk Status of AML Based on Cytogenetic and Molecular Factors

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Cytogenetic Factors</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Inv16, t(8;21), t(16;16)</td>
<td>Normal cytogenetics with isolated NPM1 variant</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal +8 only, t(9;11) only</td>
<td>c-KIT variant in patients with t(8;21) or inv16</td>
</tr>
</tbody>
</table>
## Risk Status

<table>
<thead>
<tr>
<th>Cytogenetic Factors</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other abnormalities not listed with better-risk and poor-risk cytogenetics</td>
<td>Normal cytogenetics with isolated FLT3-ITD variant</td>
</tr>
</tbody>
</table>

### Poor
- Complex (3 or more abnormalities)
  - -5, -7, 5q-, 7q-, +8, inv3, t(3;3), t(6;9), t(9;22)
- Abnormalities of 11q23, excluding t(9;11)

AML: acute myeloid leukemia; ITD: internal tandem duplication.

## 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
- Prior treatment (if any) patient has received
- Any poor risk features
- History of remission(s) and relapse(s) (if any)

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></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>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><strong>HCPCS</strong></td>
<td></td>
</tr>
<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 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</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>services; 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**

The relative importance of cytogenetic and molecular abnormalities in determining prognosis and guiding therapy is under investigation.

The ideal allogeneic donors are human leukocyte antigen -identical siblings, matched at the human leukocyte antigen-A, -B, and -DR loci (6 of 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, for which there usually is sharing of only 3 of the 6 major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

**Evidence Review**

**Description**

Acute myeloid leukemia (AML) refers to leukemias that arise from a myeloid precursor in the bone marrow. There is a high incidence of relapse, which has prompted research into various post-remission strategies using either allogeneic (allo-) or autologous hematopoietic cell transplantation (HCT). HCT refers to a procedure that infuses hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy.
Background

**Acute Myeloid Leukemia**

Acute myeloid leukemia (AML), also called acute nonlymphocytic leukemia, refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. AML is characterized by proliferation of myeloblasts, coupled with low production of mature red blood cells, platelets, and often non-lymphocytic white blood cells (granulocytes, monocytes). Clinical signs and symptoms are associated with neutropenia, thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. Approximately 21,380 new cases are diagnosed annually.49

Pathophysiology

The pathogenesis of AML is unclear. It can be subdivided by similarity to different subtypes of normal myeloid precursors using the French-American-British classification. This system classifies leukemias from M0 to M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization subsequently incorporated clinical, immunophenotypic, and a wide variety of cytogenetic abnormalities that occur in 50% to 60% of AML cases into a classification system that can be used to guide treatment according to prognostic risk categories.

Classification

The World Health Organization system recognizes five major subcategories of AML:

1. AML with recurrent genetic abnormalities;
2. AML with multilineage dysplasia;
3. Therapy-related AML and myelodysplasia;
4. AML not otherwise categorized.
5. Acute leukemia of ambiguous lineage.

AML with recurrent genetic abnormalities includes AML with t(8;21)(q22;q22), inv16(p13;q22) or t(16;16)(p13;q22), t(15;17)(q22;q12), or translocations or structural abnormalities involving 11q23. Younger patients may exhibit t(8;21) and inv16 or t(16;16). AML patients with 11q23
translocations include two subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of two or more lineages, which is associated with cytogenetic findings that include --5, 5q-, -7, 7q-, +8, +9, +11, 11q-, 12p-, -18, +19, 20q-, +21, and other translocations. AML not otherwise categorized includes disease that does not fulfill criteria for the other groups and essentially reflects the morphologic and cytochemical features and maturation level criteria used in the French-American-British classification, except for the definition of AML as having a minimum of 20% (as opposed to 30%) blasts in the marrow. AML of ambiguous lineage is diagnosed when blasts lack sufficient lineage-specific antigen expression to classify as myeloid or lymphoid.

**Genetic Abnormalities**

Molecular studies have identified a number of genetic abnormalities that can also be used to guide prognosis and management of AML. Cytogenetically normal AML is the largest defined subgroup of AML, comprising approximately 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic variants that affect outcomes, six of which have been identified. The FLT3 gene that encodes FMS-like receptor tyrosine kinase 3, a growth factor active in hematopoiesis, is mutated in 33% to 49% of cytogenetically normal AML cases; among those, 28% to 33% consist of internal tandem duplications, 5% to 14% are missense variants in exon 20 of the tyrosine kinase activation loop, and the rest are single nucleotide variants in the juxtamembrane domain. All FLT3 variants result in a constitutively activated protein and confer a poor prognosis. Several pharmaceutic agents that inhibit the FLT3 tyrosine kinase are under investigation.

**Treatment**

Complete remission can be achieved initially using induction therapy, consisting of conventional doses of combination chemotherapy. A complete response is achieved in 60% to 80% of adults younger than 60 years of age and 40% to 60% in patients older than 60 years of age. However, the high incidence of disease relapse has prompted research into a variety of post-remission (consolidation) strategies, typically using high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) or high-dose or reduced-intensity chemotherapy with allogeneic HCT (allo-HCT). The two treatments - autologous HCT and allo-HCT - represent two different strategies. The first, autologous HCT, is a “rescue,” but not a therapeutic procedure; the second, allo-HCT, is a “rescue” plus a therapeutic procedure.
**Hematopoietic Cell Transplantation**

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood is discussed in detail in a separate policy (see Related Policies).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT; however, immunologic compatibility between donor and patient is critical for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

**Conditioning for Hematopoietic Cell Transplantation**

**Conventional Conditioning for HCT**

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 cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that is mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse events. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which increases susceptibility to opportunistic infections. The immune reactivity between donor T-cells and malignant cells is responsible for the GVM effect; it also leads to acute and chronic GVHD.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiotherapy) 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. Therefore, 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 before engraftment, but not GVHD.

**Reduced-Intensity Conditioning for Allo-HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total 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. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

A 2015 review in the New England Journal of Medicine summarized recent advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments.¹

**Hematopoietic Cell Transplantation**

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood 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 detail in a separate policy (see Related Policies).
Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT; however, immunologic compatibility between donor and patient is critical for achieving a good outcome with allo-HCT. Immunologic compatibility is established by classifying human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR 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 Conditioning for HCT**

The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation; this is performed at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that is mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered 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 medically fit to tolerate substantial adverse events 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, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase susceptibility to opportunistic infections. The immune reactivity between donor T cells and malignant cells is responsible for the GVM effect; it also leads to acute and chronic GVHD.

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 when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.
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 2-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality 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 nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum—from nearly totally myeloablative to minimally myeloablative with lymphoablation—because it tailors its intensity 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 refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Summary of Evidence

For individuals who have cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia (AML) in first complete remission who receive (allo-HCT) with myeloablative conditioning, the evidence includes RCTs and matched cohort studies. The relevant outcomes are overall survival (OS) and disease-specific survival (DSS). The evidence has revealed that allo-HCT is better at improving overall and disease-specific survival rates in patients with AML in first complete remission than conventional chemotherapy. All trials employed natural randomization based on donor availability and intention-to-treat analysis. Survival rates appear to be associated with presence of minimal residual disease and risk category. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML refractory to standard induction chemotherapy who receive allo-HCT with myeloablative conditioning, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. The relevant outcomes are overall survival and disease-specific survival. The evidence would suggest that allo-HCT improves overall and disease-specific survival rates in patients who are refractory to induction chemotherapy better than conventional chemotherapy. While there are some limitations to the evidence, which include its retrospective nature, lack of rigorous randomization, and general pitfalls of registry data, these results may provide clinically meaningful benefit for such patients who do not have
other treatment options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML who relapsed after standard induction chemotherapy-induced first complete remission who receive allo-HCT or autologous HCT with myeloablative conditioning, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. The relevant outcomes are OS and disease-specific survival. The evidence has shown that allo-HCT improves OS rates in patients with relapsed AML better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission (CR1) and for medical reasons cannot tolerate myeloablative conditioning who receive allo-HCT with reduced-intensity conditioning, the evidence includes 2 RCTs and other comparative and noncomparative studies. The relevant outcomes are OS, disease-specific survival, and treatment-related morbidity. The RCTs compared reduced-intensity conditioning with myeloablative conditioning and reported similar rates in nonrelapse mortality, relapse, and OS though one of the trials was stopped prematurely due to a slow accrual of patients. Two retrospective comparative studies found no difference in OS or leukemia-free survival between the conditioning regimens. It appears unlikely that additional comparative evidence is likely be generated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML in CR1 or beyond without a suitable allo-HCT donor who receive autologous HCT, the evidence includes prospective cohort studies in which patients with an available sibling donor were offered allo-HCT (biologic randomization) with random assignment of all others to autologous HCT or chemotherapy (or no further treatment); and randomized trials comparing autologous HCT with chemotherapy in all patients. The relevant outcomes are OS and disease-specific survival. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved disease-free survival rates. The OS did not differ between the groups. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.
Table 2. 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><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT03902665</td>
<td>Up-front Hematopoietic Stem Cell Transplantation in Patients with Acute Myeloid Leukemia Aged 65-75</td>
<td>enrolling by invitation</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>NCT00342316</td>
<td>Prospective Controlled Clinical Study of Allogeneic Stem Cell Transplantation with Reduced Conditioning versus Best Standard Care in Acute Myeloid Leukemia in First Complete Remission</td>
<td>360</td>
<td>Dec 2017</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 one physician specialty society (two reviewers) and one academic medical center while this policy was under review in 2009. There was strong consensus among reviewers that allogeneic HCT with reduced-intensity conditioning was of value in patients who were in complete remission. There was general support for the policy statements.

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network

The National Comprehensive Cancer Network clinical guidelines (v.2.2020)\(^7\) for acute myeloid leukemia state that HCT is recommended for patients aged<60 years after standard-dose cytarabine induction with induction failure or significant residual disease without a hypocellular marrow or as post-remission therapy in those with intermediate-risk or poor-risk cytogenetics. Allo-HCT is recommended for patients aged ≥60 years after standard-dose cytarabine induction.
with residual disease or induction failure or following complete response (reduced-intensity HCT). In addition, allo-HCT is recommended for relapsed or refractory disease.

Under discussion are recommendations also include autologous HCT for patients who achieve second molecular remission and to reserve allogeneic transplant for those patients who have persistent disease, despite therapy for relapsed disease.

**Medicare National Coverage**

The Centers for Medicare & Medicaid Services have the following national coverage determination on use of autologous cell transplantation for AML:

- **Allogeneic**: “…for the treatment of leukemia, leukemia in remission…”
- **Autologous**: “Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched.”

**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**


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/01/00</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>
</tr>
<tr>
<td>05/13/03</td>
<td>Replace Policy - Policy updated, references added; no change in policy statement. Updated CPT codes.</td>
</tr>
<tr>
<td>08/12/03</td>
<td>Replace Policy - Policy reviewed and recommended for approval by OAP July 22, 2003; no change in policy statement.</td>
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<tr>
<td>12/14/04</td>
<td>Replace Policy - Policy updated with references, NCCN guidelines, and NCI clinical trials information. Policy statement unchanged.</td>
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<tr>
<td>01/10/06</td>
<td>Replace Policy - Policy updated with literature search; NCI information updated; no change to policy statement.</td>
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<td>06/02/06</td>
<td>Disclaimer and Scope update - No other changes</td>
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<tr>
<td>06/12/07</td>
<td>Replace Policy - Policy updated with literature review; references added. No change in policy statement. Reviewed by OAP on May 24, 2007.</td>
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<tr>
<td>10/09/07</td>
<td>Cross References Updated - No other changes.</td>
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<tr>
<td>11/11/08</td>
<td>Replace Policy - Policy extensively updated with literature search. Policy statement updated to remove “HDC” from statement and replaced with “cell transplantation”. This update also reflected in the title and throughout the policy. Investigational statement was added to include Allogeneic SCT to treat AML relapsing after prior therapy. Reviewed by OAP on May 22, 2008.</td>
</tr>
<tr>
<td>09/15/09</td>
<td>Replace Policy - Policy extensively updated with literature search. Policy statements updated to include allogeneic HCT used in patients with poor to intermediate risk AML in remission and that allogeneic HCT may be used after failed autologous HCT. References added. Reviewed by OAP on August 20, 2009.</td>
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<td>02/09/10</td>
<td>Code Update - New 2010 codes added.</td>
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<td>09/14/10</td>
<td>Replace Policy - Policy updated with literature review; references 10, 21-23 added. No change in policy statements.</td>
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<tr>
<td>10/11/11</td>
<td>Replace Policy – Policy updated with literature search; reference 12 added. No change to policy statements. ICD-9 and HCPCS codes updated; ICD-10 codes added. Title changed from “myelogenous” to “myeloid” leukemia. Codes 38220 and 38221 removed from policy.</td>
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<tr>
<td>01/24/12</td>
<td>Code 38232 added.</td>
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<td>02/10/12</td>
<td>The CPT code 38204 was removed from the policy, as it is not specific to transplant.</td>
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<tr>
<td>06/20/12</td>
<td>Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.</td>
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<td>07/30/12</td>
<td>Related Policies title updates: 8.01.21, 8.01.22, 8.01.29, 8.01.30, 8.01.31, 8.01.35, 8.01.514, and 8.01.520</td>
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<td>Replace policy. Policy updated with literature search; reference 14 added. No change in policy statements.</td>
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<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>
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<tr>
<td>10/14/13</td>
<td>Replace policy. Rationale updated based on a literature review through July 1, 2013. Reference 27 added; others renumbered/removed. Policy statements unchanged. Code 38204 removed; this is not reviewed.</td>
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<tr>
<td>12/06/13</td>
<td>Update Related Policies. Remove 8.01.31 as it was archived.</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. Remove 8.01.20 and add 8.01.529.</td>
</tr>
<tr>
<td>06/24/14</td>
<td>Update Related Policies. Remove 8.01.35 and 8.01.42, then add 8.01.530 and 8.01.532.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>11/20/14</td>
<td>Annual Review. Policy updated with literature review through June 18, 2014; references 13, and 35-36 added. No change to policy statements. ICD-9 and ICD-10 diagnosis and procedure codes removed; they do not relate to adjudication of the policy.</td>
</tr>
<tr>
<td>11/10/15</td>
<td>Annual Review. Policy updated with literature review through July 9, 2015; no references added. Policy statements updated with clarifying information and to align with other HCT policies but the intent remains unchanged.</td>
</tr>
<tr>
<td>05/01/16</td>
<td>Annual Review, approved April 12, 2016. Policy updated with literature review through December 13, 2015; references 2-3 and 35 added. Policy statements unchanged.</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 38240 and 38241.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references 16-17 and 49-51 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Annual Review, approved March 5, 2019. Policy updated with literature review through October 2018; reference 48 added. Policy statement regarding medical necessity for auto-HCT changed to clarify that it applies to patients that are not candidates for allo-HCT. Investigational statements added for patients not meeting medical necessity criteria.</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). ©2020 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.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDeptInquiries@Premera.com

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 because of race, color, national origin, age, disability or sex.

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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 http://www.hhs.gov/ocr/office/file/index.html

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).

Arabic (Arabic):

يجوز هذا الإشعار معلومات هامة. قد يحتوي هذا الإشعار معلومات متعلقة بحقوقكم. قد تكون هناك تأثيرات على أقراراتكم في هذا الإشعار. قد تكون الإشارة للمعالجة المعنية في لغة الإشارة التي تستخدمها للمساعدة في فهمك. يحق لك الحصول على هذه المعلومات والمساعدة بكلمات أخرى تعرفها. الرجاء مراجعة رقم المو可能です 800-722-1471 (TTY: 800-842-5357).

Chinese (Chinese):

本通知有重要的讯息。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。請撥電話 800-722-1471 (TTY: 800-842-5357).

Cushite (Oromo) (Cushite):


Deutsche (German):


Hmoob (Hmong):


Ilokano (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalwin nga adda ket naglaon iti napateg nga impormasion maihanggip iti aplikasyowo nyo coverage babanen ti Iti Premera Blue Cross. Daytoy ket mabalbin dagiti importante a petsa iti daytoy a pakdaar. Mabalbin nga adda rumbang nga ariyadiy nga aadda sakyab dagiti partikular a naituding nga adda tawon tapo mapagonladay ngi coverage ti saluy-an nga tungon kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tungon ti bukoday nga pasagasso nga awan ti bayadayan. Tumawg ngi numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

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 debo 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).


ไทย (Thai): ประกาศนี้มีข้อมูลที่สำคัญเกี่ยวกับการขอรับการสนับสนุนการเงินจากโครงการประกันภัย Life Mast. การขอรับการสนับสนุนการเงินจากโครงการประกันภัย Life Mast สำหรับการพักการเงินหรือการสนับสนุนการเงิน เพื่อให้คุณได้รับการช่วยเหลือทางการเงินที่สำคัญที่คุณต้องการได้อย่างรวดเร็ว โปรดติดต่อกับ Premera Blue Cross หรือฝ่ายช่วยเหลือทางการเงินที่เกี่ยวข้องเพื่อขอรับการช่วยเหลือทางการเงิน.