Allogeneic hematopoietic stem-cell transplantation (HSCT) using a myeloablative conditioning regimen may be considered medically necessary to treat:

- poor- to intermediate-risk AML (Acute Myeloid Leukemia) in first complete remission (CR1) (see Policy Guidelines for information on risk stratification); 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 HSCT, but can be brought into CR with intensified induction chemotherapy and are medically able to tolerate the procedure.

Allogeneic HSCT 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 (see Policy Guidelines).

Autologous HSCT may be considered medically necessary to treat AML in CR1 or beyond or relapsed AML if responsive to intensified induction chemotherapy.

Policy Guidelines

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 (FAB) 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 (e.g., myelodysplasia)
- Presence of circulating blasts at the time of diagnosis
- Difficulty in obtaining first complete remission with standard chemotherapy
- Leukemias with monocytoid differentiation (FAB 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 in an attempt to construct a classification that is universally applicable and prognostically valid. The WHO system was adapted by the National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management, as shown in the following table:

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Cytogenetic Factors</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>inv(16), t(8;21), t(16;16)</td>
<td>Normal cytogenetics with isolated NPM1 mutation</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal</td>
<td>C-KIT mutation in patients with t(8;21) or inv(16)</td>
</tr>
<tr>
<td></td>
<td>+8 only, t(9;11) only</td>
<td>Other abnormalities not listed with better-risk and poor-risk cytogenetics</td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (3 or more abnormalities)</td>
<td>Normal cytogenetics with isolated FLT3-ITD mutations</td>
</tr>
<tr>
<td></td>
<td>-5, -7, 5q-, 7q-, +8, inv3, t(3;3), t(6;9), t(9;22)</td>
<td>Abnormalities of 11q23, excluding t(9;11)</td>
</tr>
</tbody>
</table>

AML: acute myeloid leukemia

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 (HLA)–identical siblings, matched at the HLA-A, -B, and -DR loci (6 of 6). Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor identified through the National
Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, 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 and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Cross-reference:
- MP-9.038 Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
- MP-9.039 Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
- MP-9.041 Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia
- MP-9.042 Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
- MP-9.043 Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
- MP-9.044 Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- MP-9.045 Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
- MP-9.046 Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia
- MP-9.047 Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer
- MP-9.048 Hematopoietic Stem-Cell Transplantation Miscellaneous Solid Tumors in Adults
- MP-9.049 Hematopoietic Stem-Cell Transplantation for Breast Cancer
- MP-9.050 Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- MP-9.052 Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors
- MP-9.053 Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
- MP-9.054 Hematopoietic Stem-Cell Transplantation for Solid Tumors of Children
- MP-9.055 Allogeneic HSCT for Genetic Diseases and Acquired Anemias
- MP-9.056 Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to the Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) 110.8.1, Stem Cell Transplantation.

**The Federal Employee Program (FEP) may include specific conditions in which autologous and nonmyeloablative (reduced-intensity conditioning or RIC) allogeneic blood or marrow stem cell transplants may be considered eligible for coverage. Refer to the Service Plan Benefit Brochure for covered indications.

III. DESCRIPTION/BACKGROUND

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. There is a high incidence of relapse, which has prompted research into a variety of post-remission strategies using either allogeneic or autologous hematopoietic stem-cell transplantation (HSCT). HSCT 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 drugs with or without whole-body radiotherapy.

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) may use stem cells obtained from the transplant recipient (autologous HSCT) or from a related or unrelated donor (allogeneic HSCT [allo-HSCT]). 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 “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in MP 9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.

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

Complete remissions can be achieved initially using conventional doses of combination chemotherapy in up to 80% of acute myeloid leukemia (AML) patients. However, the high
incidence of disease relapse has prompted research into a variety of postremission (consolidation) strategies, typically using high-dose chemotherapy with autologous HSCT or high-dose or reduced-intensity chemotherapy with allo-HSCT. As outlined next, the 2 treatments—autologous HSCT and allo-HSCT—represent 2 different strategies. The first, autologous HSCT, is a “rescue,” but not a therapeutic procedure; the second, allo-HSCT, is a “rescue” plus a therapeutic procedure.

**Conventional Preparative Conditioning for HSCT**

The conventional (“classical”) practice of allo-HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect 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 to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increase the patient’s susceptibility to opportunistic infections.

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

**Reduced-Intensity Conditioning for Allo-HSCT**

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 nonrelapse 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, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HSCT 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, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**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 13,000 new cases are diagnosed annually.

The pathogenesis of AML is unclear. It can be subdivided according to resemblance to different subtypes of normal myeloid precursors using the French-American-British (FAB) classification system. This system classifies leukemias from M0–M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization (WHO) 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.

The WHO system recognizes 5 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; and (5) acute leukemia of ambiguous lineage. AML with recurrent genetic abnormalities includes AML with t(8;21)(q22;q22), inv(16)(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 inv(16) or t(16;16). AML patients with 11q23 translocations include 2 subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of 2 lineages or more, which is associated with cytogenetic findings that include -7/del(7q), -5/del(5q), +8, +9, +11, del(11q), del(12p), -18, +19, del(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 FAB 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.

Molecular studies have identified a number of genetic abnormalities that also can be used to guide prognosis and management of AML. Cytogenetically normal AML (CN-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 mutations that affect outcomes, 6 of which have been identified. The FLT3 gene that encodes FMS-like receptor tyrosine kinase (TK) 3, a growth factor active in hematopoiesis, is mutated in 33% to 49% of CN-AML cases; among those, 28% to 33% consist of internal tandem duplications (ITD), 5% to 14% are missense mutations in exon 20 of the TK activation loop, and the rest are point mutations.
mutations in the juxtamembrane domain. All FLT3 mutations result in a constitutively activated protein and confer a poor prognosis. Several pharmaceutic agents that inhibit the FLT3 TK are under investigation.

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.

IV. RATIONALE

The most recent literature review for this policy was performed for the period June 18, 2014, through December 13, 2015.

Hematopoietic stem cell transplantation (HSCT) has been investigated as consolidation therapy for patients whose disease enters complete remission following initial induction treatment. It also is used as salvage therapy in patients who experience disease relapse or have disease refractory to induction chemotherapy. The following evidence review is organized primarily according to stem cell source and setting (i.e., consolidation, refractory disease, salvage).

A 2015 review in the New England Journal of Medicine summarizes recent advances in the classification of acute myeloid leukemia (AML), the genomics of AML and prognostic factors, and current and new treatments.¹

Allogeneic HSCT for Chemotherapy-Responsive Consolidation

Systematic Reviews and Meta-Analyses
A 2015 meta-analysis examined prospective trials of adult patients with intermediate-risk AML in first complete remission (CR1) who underwent HSCT.² The analysis included 9 prospective, controlled studies that enrolled a total of 1950 patients between the years 1987 and 2011 (study size range, 32-713 patients). Allogeneic HSCT (allo-HSCT) was associated with significantly better relapse-free survival (RFS), overall survival (OS), and relapse rate than autologous HSCT and/or chemotherapy (hazard ratio [HR], 0.684; 95% confidence interval [CI], 0.48 to 0.95; HR=0.76; 95% CI, 0.61 to 0.95; HR=0.58; 95% CI, 0.45 to 0.75, respectively). Treatment-related mortality (TRM) was significantly higher following allo-HSCT than autologous HSCT (HR=3.09; 95% CI, 1.38 to 6.92). However, a subgroup analysis which used updated criteria to define intermediate risk AML showed no OS benefit for allo-HSCT over autologous HSCT (HR=0.99; 95% CI, 0.70 to 1.39).

A meta-analysis of allo-HSCT in patients with AML in CR1 pooled data from 5 studies that included a total of 3100 patients.³ Among those patients, 1151 received allo-HSCT and 1949
were given alternative therapies including chemotherapy and autologous HSCT. All studies employed natural randomization based on donor availability and intention-to-treat analysis, with OS and disease-free survival (DFS) as outcomes of interest. This analysis showed a significant advantage of allo-HSCT in terms of OS for the entire cohort (fixed-effects model HR=1.17; 95% CI, 1.06 to 1.30; p=0.003; random-effects model HR=1.15; 95% CI, 1.01 to 1.32; p=0.037) even though none of the individual studies did so. Meta-regression analysis showed that the effect of allo-HSCT on OS differed depending on the cytogenetic risk groups of patients, suggesting significant benefit for poor-risk patients (HR=1.39, 95% CI not reported), indeterminate benefit for intermediate-risk cases, and no benefit in better-risk patients compared with alternative approaches. The authors cautioned that the compiled studies used different definitions of risk categories (e.g., SWOG, Medical Research Council, European Organization for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell’ Adulto), but examination shows cytogenetic categories in those definitions are very similar to recent guidelines from the National Comprehensive Cancer Network (NCCN). Furthermore, the statistical power of the meta-regression analysis was limited by small numbers of cases. However, the results of this meta-analysis are supported in general by data compiled in other reviews.

Evidence from the meta-analysis suggests patients with cytogenetically defined better prognosis disease may not realize a significant survival benefit with allo-HSCT in CR1 that outweighs the risk of associated morbidity and nonrelapse mortality (NRM). However, there is considerable genotypic heterogeneity within the 3 World Health Organization cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics. For example, patients with better-prognosis disease (e.g., core-binding factor AML) based on cytogenetics, and a mutation in the c-KIT gene of leukemic blast cells, do just as poorly with postremission standard chemotherapy as patients with cytogenetically poor-risk AML. Similarly, patients with cytogenetically normal AML (intermediate prognosis disease) can be subcategorized into groups with better or worse prognosis based on the mutational status of the nucleophosmin gene (NPM1) and the FLT3 gene (defined earlier in the Background). Thus, patients with mutations in NPM1 but without FLT3-ITD (internal tandem duplications) have postremission outcomes with standard chemotherapy that are similar to those with better prognosis cytogenetics; in contrast, patients with any other combination of mutations in those genes have outcomes similar to those with poor prognosis cytogenetics. These examples highlight the rapidly growing body of evidence for genetic mutations as additional predictors of prognosis and differential disease response to different treatments. It follows that, because the earlier clinical trials compiled in the meta-analysis described here did not account for genotypic differences that affect prognosis and alter outcomes, it is difficult to use the primary trial results to draw conclusions concerning the role of allo-HSCT in different patient risk groups.

A meta-analysis incorporated data from 24 trials involving a total of 6007 patients who underwent allo-HSCT in CR1. Among the total, 3638 patients were stratified and analyzed according to cytogenetic risk (547 good-, 2499 intermediate-, 592 poor-risk patients with AML, respectively) using a fixed-effects model. Compared with either autologous HSCT or additional consolidation chemotherapy, the HR for OS among poor-risk patients across 14 trials was 0.73.
(95% CI, 0.59 to 0.90; p<0.01); among intermediate-risk patients across 14 trials, the HR for OS was 0.83 (95% CI, 0.74 to 0.93; p<0.01); and among good-risk patients across 16 trials, the HR for OS was 1.07 (95% CI, 0.83 to 1.38; p=0.59). Interstudy heterogeneity was not significant in any of these analyses. Results for DFS were very similar to those for OS in this analysis. These results concur with those from the previously cited meta-analysis for use of allo-HSCT as consolidation therapy for AML.

Clinical Studies
A 2014 study compared outcomes for 185 matched pairs from a large multicenter trial (AMLCG99). Patients younger than 60 years who underwent allo-HSCT in CR1 were matched to patients who received conventional postremission chemotherapy. The main matching criteria were AML type, cytogenetic risk group, patient age, and time in CR1. In the overall pairwise-compared AML population, the projected 7-year OS rate was 58% for the allo-HSCT and 46% for the conventional postremission treatment group (log-rank test, p=0.037). Relapse-free survival was 52% in the allo-HSCT group and 33% in the control group (p<0.001). OS was significantly better for allo-HSCT in patient subgroups with nonfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome (MDS). For the entire patient cohort, postremission therapy was an independent factor for OS (HR=0.66; 95% CI, 0.49 to 0.89 for allo-HSCT vs conventional chemotherapy), among age, cytogenetics, and bone marrow blasts after the first induction cycle.

Autologous HSCT for Chemotherapy-Responsive Consolidation

Systematic Reviews and Meta-Analyses
A meta-analysis published in 2004 examined survival outcomes of autologous HSCT in CR1 versus standard chemotherapy or no further treatment in AML patients aged 15 to 55 years. Two types of studies were eligible: (1) prospective cohort studies in which patients with an available sibling donor were offered allo-HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and (2) randomized trials that compared autologous HSCT with chemotherapy in all patients. Among a total of 4058 patients included in 6 studies, 2989 (74%) achieved CR1; 1044 (26%) were randomly allocated to HSCT (n=524) or chemotherapy (n=520). Of the 5 studies for which OS data were available, outcomes with autologous HSCT were better in 3, and outcomes with chemotherapy were better in 2. None of the differences were statistically significant, nor was the pooled estimate (fixed-effects model survival probability ratio, 1.01; 95% CI, 0.89 to 1.15; p=0.86). In all 6 studies, DFS was numerically superior with autologous HSCT compared with chemotherapy (or no further treatment), but only 1 reported a statistically significant DFS probability associated with autologous HSCT. However, the pooled estimate for DFS showed a statistically significant probability in favor of autologous HSCT at 48 months posttransplant (fixed-effects model survival probability ratio, 1.24; 95% CI, 1.06 to 1.44; p=0.006).

There are several reasons why this meta-analysis did not demonstrate a statistically significant OS advantage for autologous HSCT compared with chemotherapy given the significant estimate...
for DFS benefit. First, the pooled data showed a 6.45% greater NRM rate in autologous HSCT recipients compared with chemotherapy recipients. Second, 14% of chemotherapy recipients whose disease relapsed ultimately achieved a sustained second remission after undergoing an allogeneic or autologous HSCT. The intention-to-treat analysis in the studies, which included the latter cases in the chemotherapy group, may have inappropriately inflated OS rates favoring chemotherapy. Furthermore, this analysis did not take into account potential effects of cytogenetic or molecular genetic differences among patients that are known to affect response to treatment. Finally, the dataset comprised studies performed between 1984 and 1995, during which transplant protocols and patient management evolved significantly, particularly compared with current care.

A second meta-analysis published in 2010 evaluated autologous HSCT versus further chemotherapy or no further treatment for AML in CR1. A total of 9 randomized trials involving 1104 adults who underwent autologous HSCT and 1118 who received additional chemotherapy or no additional treatment were identified. The analyses suggested that autologous HSCT in CR1 is associated with statistically significant reduction of relapse risk (RR=0.56; 95% CI, 0.44 to 0.71; p=0.001) and significant improvement in DFS (HR=0.89; 95% CI, 0.80 to 0.98), but at the cost of increased NRM (RR=1.90; 95% CI, 1.34 to 2.70; p=0.23). There were more deaths during the first remission among patients assigned to autologous HSCT than among the chemotherapy recipients or further untreated patients. As a consequence of increased NRM, no statistical difference in OS (HR=1.05; 95% CI, 0.91 to 1.21) was associated with the use of autologous HSCT, compared with further chemotherapy or no further therapy. These results were concordant with the earlier meta-analysis.

**Clinical Studies**

A prospective, randomized phase 3 trial compared autologous HSCT plus intensive consolidation chemotherapy among patients (range, 16-60 years) with newly diagnosed AML of similar risk profiles in CR1. Patients in CR1 after 2 cycles of intensive chemotherapy (etoposide and mitoxantrone), who were not candidates for allo-HSCT, were randomly allocated between a third consolidation cycle of the same chemotherapy (n=259) or autologous HSCT (n=258). The HSCT group showed a trend toward superior relapse-free survival, the primary outcome, compared with chemotherapy recipients at 5 years (38% vs 29%, respectively, p=0.065. HSCT patients also had a lower relapse rate at 5 years compared with chemotherapy recipients (58% vs 70%, respectively, p=0.02). OS did not differ between HSCT and chemotherapy recipients, respectively (44% vs 41%, respectively, p=0.86). NRM was more frequent in the autologous HSCT group than in the chemotherapy consolidation group (4% vs 1%, respectively, p=0.02). Despite this difference in NRM, the relative equality of OS rates was attributed by the investigators to a higher proportion of successful salvage treatments—second-line chemotherapy, autologous or allo-HSCT—in the chemotherapy consolidation recipients that were not available to the autologous HSCT patients. This large study shows an advantage for postremission autologous HSCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy-consolidated patients.
Allo-HSCT for Primary Refractory AML

Conventional-dose induction chemotherapy will not produce remission in 20% to 40% of patients with AML, connoting refractory AML. An allo-HSCT using a matched related donor (MRD) or matched unrelated donor (MUD) represents the only potentially curative option for these patients. In several retrospective studies, OS rates have ranged from 13% at 5 years to 30% at 3 years, although this procedure is accompanied by NRM rates of 25% to 62% in this setting. For patients who lack a suitable donor (MRD or MUD), alternative treatments include salvage chemotherapy with high-dose cytarabine or etoposide-based regimens, monoclonal antibodies (e.g., gemtuzumab ozogamicin), multidrug resistance modulators, and other investigational agents (e.g., FLT3 antagonists). Because it is likely that stem cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, upfront autologous HSCT has no role in patients who fail induction therapy.

Allogeneic or Autologous HSCT for Relapsed AML

Most patients with AML will experience disease relapse after attaining a CR1. Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved. Retrospective data compiled from 667 of 1540 patients entered in 3 phase 3 trials suggest allo-HSCT in CR2 can produce 5-year OS rates of 26% to 88%, depending on cytogenetic risk stratification. Because reinduction chemotherapy treatment may be associated with substantial morbidity and mortality, patients whose disease has relapsed and who have a suitable donor may proceed directly to allo-HSCT. In patients without an allogeneic donor, or those who are not candidates for allo-HSCT due to age or other factors, autologous HSCT may achieve prolonged DFS in 9% to 55% of patients in CR2 depending on risk category. However, because it is likely that stem cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, and it is often difficult to achieve CR2 in these patients, autologous HSCT in this setting is usually limited to patients who have a sufficient stem cell preparation remaining from collection in CR1.

Allo-HSCT is often performed as salvage for patients who have relapsed after conventional chemotherapy or autologous HSCT. The decision to attempt reinduction or proceed directly to allo-HSCT is based on the availability of a suitable stem cell donor and the likelihood of achieving remission, the latter being a function of cytogenetic risk group, duration of CR1, and the patient’s health status. Registry data show DFS rates of 44% using sibling allografts and 30% with MUD allografts at 5 years for patients transplanted in CR2, and DFS of 35% to 40% using sibling transplants and 10% with MUD transplants for patients with induction failure or in relapse following HSCT.

Reduced-Intensity Conditioning Allo-HSCT

A body of evidence is accruing from clinical studies that reduced-intensity conditioning (RIC) with allo-HSCT may be used for consolidation therapy in patients with AML.
A 2014 meta-analysis compared RIC and myeloablative conditioning regimens for allo-HSCT in patients with AML (and acute lymphoblastic leukemia). The analysis included 23 clinical trials reported between 1990 and 2013, with approximately 15,000 adult patients. Eleven studies included AML and myelodysplastic syndrome (MDS) and 5 included AML only. A subanalysis from 13 trials in patients with AML or MDS showed that OS was comparable in patients who received either reduced-intensity or myeloablative transplants, and the 2-year or less and 2-year or greater OS rates were equivalent between the 2 groups. The 2- to 6-year PFS, nonrelapse mortality, and acute and chronic graft-versus-host disease (GVHD) rates were reduced after RIC-HSCT, but relapse rate was increased. Similar outcomes were observed regardless of disease status at transplantation. Among the RIC-HSCT recipients, survival rates were superior if patients were in CR at transplantation.

A randomized comparative trial in matched patient groups compared the net health benefit of allo-HSCT with RIC to myeloablative conditioning. In this study, patients (age, 18-60 years) were randomly assigned to receive either 4 doses of RIC (n=99) at 2 Gy of total body irradiation plus fludarabine 150 mg/m² or 6 doses of standard conditioning (n=96) at 2 Gy of total body irradiation plus cyclophosphamide 120 mg/kg. All patients received cyclosporine and methotrexate as prophylaxis against GVHD. The primary end point was the incidence of NRM analyzed in the intention-to-treat population. This unblinded trial was stopped early because of slow accrual of patients. The incidence of NRM did not differ between the RIC and standard conditioning groups (cumulative incidence at 3 years, 13% [95% CI, 6% to 21%] vs 18% [95% CI, 10% to 26%]; HR=0.62 [95% CI, 0.30 to 1.31], respectively). Relapse cumulative incidence at 3 years was 28% (95% CI, 19% to 38%) in the RIC group and 26% (95% CI, 17% to 36%; HR=1.10; 95% CI, 0.63 to 1.90) in the standard conditioning group. DFS at 3 years was 58% (95% CI, 49% to 70%) in the RIC group and 56% (95% CI, 46% to 67%; HR=0.85; 95% CI, 0.55 to 1.32) in the standard conditioning group. OS at 3 years was 61% (95% CI, 50% to 74%) and 58% (95% CI, 47% to 70%); HR was 0.77 (95% CI, 0.48 to 1.25) in the RIC and the standard conditioning groups, respectively. No outcomes differed significantly between groups. Grade 3-4 oral mucositis was less common in the RIC group (50 patients) than in the standard conditioning group (73 patients); the frequency of other adverse effects such as GVHD and increased concentrations of bilirubin and creatinine did not differ significantly between groups.

In a comparative study, outcomes were compared in children with AML who underwent allo-HSCT using RIC regimens or myeloablative conditioning regimens. A total of 180 patients were evaluated, 39 who underwent RIC and 141 who received myeloablative regimens. Univariate and multivariate analyses showed no significant differences in the rates of acute and chronic GVHD, leukemia-free survival, and OS between treatment groups. The 5-year probabilities of OS with RIC and myeloablative regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were not higher with RIC than with myeloablative conditioning (MAC) regimens (39% vs 39%; p=0.95), and recipients of MAC regimens were not at higher risk for transplant-related mortality compared with recipients of RIC regimens (16% vs 16%; p=0.73).
A phase 2 single-center, randomized toxicity study compared MAC and RIC in allo-HSCT to treat AML. Adult patients 60 years of age or younger with AML were randomly assigned (1:1) to treatment with RIC (n=18) or MAC (n=19) for allo-HSCT. A maximum median mucositis grade of 1 was observed in the RIC group compared with grade 4 in the MAC group (p<0.001). Hemorrhagic cystitis occurred in 8 (42%) of the patients in the MAC group and none (0%) in the RIC group (p<0.01). Results of renal and hepatic tests did not differ significantly between the groups. RIC-treated patients had faster platelet engraftment (p<0.01) and required fewer erythrocyte and platelet transfusions (p<0.001) and less total parenteral nutrition than those treated with MAC (p<0.01). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18) (p=0.02). Donor chimerism was similar in the 2 groups for CD19 and CD33, but was delayed for CD3 in the RIC group. Five-year treatment-related morbidity was approximately 11% in both groups, and rates of relapse and survival did not differ significantly. Patients in the MAC group with intermediate cytogenetic AML had a 3-year survival of 73% compared with 90% among those in the RIC group.

Ongoing and Unpublished Clinical Trials
Fourteen currently unpublished trials might influence this review.

Summary of Evidence
The evidence for allogeneic hematopoietic stem cell transplantation (allo-HSCT) with myeloablative conditioning in individuals who have cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia (AML) in first complete remission includes randomized controlled trials (RCTs) and matched cohort studies. Relevant outcomes are overall survival and disease-specific survival. The evidence shows allo-HSCT in this setting improves overall and disease-specific survival rates better than conventional chemotherapy. All trials employed natural randomization based on donor availability and an intention-to-treat analysis. Although the selected studies used a range of definitions of risk categories produced by different cooperative groups (e.g., SWOG, Medical Research Council, European Organisation for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell’ Adulto), cytogenetic categories in those definitions are very similar to recent guidelines from the National Comprehensive Cancer Network.

The evidence for allo-HSCT with myeloablative conditioning in individuals who have AML refractory to induction chemotherapy or relapses after autologous HSCT but can be brought into remission with intensified chemotherapy includes retrospective data compiled from patients entered in phase 3 trials and registry data. Relevant outcomes are overall survival and disease-specific survival. The evidence suggests allo-HSCT in this setting improves overall and disease-specific survival rates better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data.

The evidence for allo-HSCT with myeloablative conditioning in individuals who have AML in second complete remission and beyond includes retrospective data compiled from patients entered in phase 3 trials and registry data. Relevant outcomes are overall survival and disease-specific survival. The evidence shows allogeneic HSCT in this setting improves OS rates better
than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data.

The evidence for allo-HSCT with reduced-intensity conditioning (RIC) in individuals who have AML in first complete remission or beyond and who otherwise would be candidates for an allogeneic transplant includes RCT and other comparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. RIC with allo-HSCT has not been directly compared with conventional chemotherapy, which is the standard of care in patients with AML for whom myeloablative chemotherapy and allo-HSCT are contraindicated. Indirect comparison of results from nonrandomized studies or comparative studies is compromised by heterogeneity among patients, treatments, outcome measures, and insufficient follow-up. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for autologous HSCT in individuals who have AML in first complete remission or beyond but do not have a suitable allogeneic donor includes prospective cohort studies in which patients with an available sibling donor were offered allo-HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and randomized trials comparing autologous HSCT to chemotherapy in all patients. Relevant outcomes are overall survival and disease-specific survival. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

**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 physician specialty society (2 reviewers) and 1 academic medical center while this policy was under review for February 2009. There was strong consensus among reviewers that RIC allo-HSCT 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 (NCCN) clinical practice guideline (v.1.2016) for AML is generally consistent with this review.40

The NCCN guideline states that HSCT in the context of a clinical trial or best supportive care is recommended for patients with induction failure. Also, a matched unrelated donor search, including umbilical cord blood should be initiated for high-risk patients who are eligible for HSCT in first complete remission, or considered at first relapse in appropriate patients concomitant with reinduction therapy. Recommendations also include autologous HSCT in patients who achieve second molecular remission, and to reserve allogeneic transplant for those patients who have persistent disease, despite therapy for relapsed disease.
U.S. Preventive Services Task Force Recommendations
Not applicable.

V. DEFINITIONS
NA

VI. BENEFIT VARIATIONS
The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER
Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION
Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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IX. REFERENCES


leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. Apr 10 2010;28(11):1878-1887. PMID 20212255


Other Sources
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Taber’s Cyclopedic Medical Dictionary 21st edition

Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) NCD 110.8.1 Stem Cell Transplantation Effective 8/4/2010. CMS [Website]:

X. POLICY HISTORY

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