Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage hematopoietic cell transplantation for acute myeloid leukemia when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

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

Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen may be considered **medically necessary** to treat:
- poor- to intermediate-risk AML in remission (CR1) (see Considerations for information on risk stratification), or
- AML that relapses following chemotherapy-induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy; or
- AML that is refractory to, or relapses following, standard induction chemotherapy but can be brought into CR 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 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 Considerations).

When Policy Topic is not covered

Hematopoietic stem-cell transplantation for acute myeloid leukemia is not covered if the criteria are not met.

Considerations

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:

Risk Status of AML Based on Cytogenetic and Molecular Factors

Risk Status	Cytogenetic Factors	Molecular Abnormalities
Favorable	Inv(16), t(8;21), t(16;16)	Normal cytogenetics with isolated NPM1 mutation
Intermediate	Normal +8 only, t(9;11) only Other abnormalities not listed with better-risk and poor-risk cytogenetics	c-KIT mutation in patients with t(8;21) or inv(16)
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)	Normal cytogenetics with isolated FLT3-ITD mutations

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 HLA-identical siblings, matched at the HLA-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, where usually there is sharing of only 3 of the 6 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.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: • With cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia in first complete remission	Interventions of interest are: • Allogeneic hematopoietic cell transplantation with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With acute myeloid leukemia refractory to standard induction chemotherapy	Interventions of interest are: • Allogeneic hematopoietic cell transplantation with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With acute myeloid leukemia who relapsed after standard induction chemotherapy	Interventions of interest are: • Allogeneic or autologous hematopoietic cell transplantation with myeloablative conditioning	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • With cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia in remission and cannot tolerate myeloablative conditioning	Interventions of interest are: • Allogeneic hematopoietic cell transplantation with reduced-intensity conditioning	Comparators of interest are: • Myeloablative conditioning allogeneic hematopoietic cell transplantation • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related morbidity
Individuals: • With acute myeloid leukemia in remission without suitable allogeneic hematopoietic cell transplantation donor	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Conventional chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival

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 postremission 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.

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission who receive allo-HCT with myeloablative conditioning (MAC), the evidence includes randomized controlled trials and matched cohort studies. Relevant outcomes are overall survival and disease-specific survival. 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 an intention-to-treat analysis. Survival rates appear to be associated with the 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 MAC, the evidence 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 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 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 MAC, the evidence 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 has shown that allo-HCT improves overall survival 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 and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning, the evidence includes 2 randomized controlled trials, 2 meta-analyses, and other comparative and noncomparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. The randomized controlled trials compared reduced-intensity conditioning with MAC and reported similar rates in nonrelapse mortality, relapse, and overall survival though one of the trials was stopped prematurely due to a slow accrual of patients. Two retrospective comparative studies found no difference in overall survival or leukemia-free survival between the conditioning regimens. It appears unlikely that additional comparative evidence will 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 first complete remission 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. Relevant outcomes are overall and disease-specific survival. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved disease-free survival rates. Overall survival 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.

Background
Acute Myeloid Leukemia
Acute myeloid leukemia (AML), also called acute nonlymphocytic leukemia, AML 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.[1]

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 system. 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 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), 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 2 subgroups: AML in infants and therapy-related leukemia. Multilineage dysplasia AML must exhibit dysplasia in 50% or more of the cells of 2 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 also can 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 (SNVs) 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 in 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 postremission (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 2 treatments—autologous HCT and allo-HCT—represent 2 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
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 "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in a separate policy.

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.

A 2015 review in the *New England Journal of Medicine* has summarized recent advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments.[2]

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.

Rationale

This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through November 6, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Hematopoietic cell transplantation (HCT) 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. This evidence review discusses the following uses and conditions of HCT: consolidation therapy with allogeneic HCT (allo-HCT) during first complete remission (CR1), salvage therapy for refractory acute myeloid leukemia (AML), therapy for relapsed AML, reduced-intensity conditioning (RIC), and consolidation therapy with autologous HCT.

Allo-HCT for Chemotherapy-Responsive Consolidation

Systematic Reviews
A 2015 meta-analysis examined prospective trials of adults with intermediate-risk AML in CR1 who underwent HCT.[3] The analysis included 9 prospective, controlled studies that enrolled 1950 patients between the years 1987 and 2011 (sample range, 32-713 patients). Allo-HCT was associated with significantly better relapse-free survival (RFS), overall survival (OS), and relapse rate than autologous HCT and/or chemotherapy (hazard ratio [HR], 0.68; 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 was significantly higher following allo-HCT than autologous HCT (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-HCT over autologous HCT (HR=0.99; 95% CI, 0.70 to 1.39).

A 2009 systematic review incorporated data from 24 trials involving 6007 patients who underwent allo-HCT in CR1.[4] Among the total, 3638 patients were stratified and analyzed according to cytogenetic risk (547 good-, 2499 intermediate-, 592 poor-risk patients with AML) using a fixed-effects model. Compared with either autologous HCT 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 disease-free survival (DFS) were very similar to those for OS in this analysis. These results are in line with those from another meta-analysis[5] on the use of allo-HCT as consolidation therapy for AML.

A 2005 meta-analysis of allo-HCT in patients with AML in CR1 pooled data from 5 studies (total N=3100 patients).[5] Among those patients, 1151 received allo-HCT, and 1949 were given alternative therapies including chemotherapy and autologous HCT. All studies employed natural randomization based on donor availability and intention-to-treat analysis, with OS and DFS as outcomes of interest. This analysis showed a significant advantage for allo-HCT regarding 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-HCT on OS differed depending on the cytogenetic risk groups of patients, suggesting a 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. Reviewers cautioned that the compiled studies used different definitions of risk categories than other groups (eg, SWOG, Medical Research Council, European Organisation for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell' Adulto)[6] Although the statistical power of the meta-regression analysis was limited by small numbers of cases, the results of this meta-analysis are supported in general by data from other reviews.[7-10]

Evidence from the meta-analysis suggests patients with better prognosis (as defined by cytogenetics) may not realize a significant survival benefit with allo-HCT in CR1 that outweighs the risk of associated morbidity and nonrelapse mortality. 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.[11] For example, patients with better prognosis disease (eg, core-binding factor AML) based on cytogenetics, and a variant in the *KIT* gene of leukemic blast cells, do just as poorly with postremission standard chemotherapy as patients with cytogenetically poor-risk AML.[12] 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 (the *FLT3* gene, as defined in the Background section, is a gene that encodes FMS-like receptor tyrosine kinase 3, a growth factor active in hematopoiesis). Thus, patients with variants in *NPM1* but without *FLT3* 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 variants in those genes have outcomes similar to those with poor prognosis cytogenetics.[13] 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 on the role of allo-HCT in different patient risk groups.

A meta-analysis by Buckley et al (2017) evaluated the relation between minimal residual disease (MRD) at the time of HCT and posttransplantation outcomes.[14] The literature search, conducted through June 2016, identified 19 studies (total N=1431 patients) for inclusion. Risk of bias was assessed using a modified version of Quality of Prognostic Studies instrument, which focused on: prognostic factor measurement, study confounding, and statistical analysis and reporting. Five studies were considered at high risk for bias, nine were at moderate risk, and five were at low risk. The following variables were collected from each study: age, follow-up, adverse-risk cytogenetics, conditioning type (myeloablative or reduced-intensity), MRD detection method, and survival. Reviewers reported that the presence of MRD at the time of transplantation was associated with higher relapse and mortality. This association was seen regardless of patient age and type of conditioning, which suggests that an intense conditioning regimen may not be able to overcome the adverse impact of MRD.

Prospective Studies
A 2014 study compared outcomes of 185 matched pairs from a large multicenter trial (AMLCG99).[15] Patients younger than 60 years of age who underwent allo-HCT 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-HCT and 46% for the conventional postremission treatment group (p=0.037). The RFS rate was 52% in the allo-HCT group and 33% in the control group (p<0.001). OS was significantly longer for allo-HCT patient subgroups with nonfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome. 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-HCT vs conventional chemotherapy) among age, cytogenetics, and bone marrow blasts after the first induction cycle.

Retrospective Studies
In 2017, Heidrich et al conducted retrospective analyses of subgroups from 2 prospective clinical trials, including 497 patients with intermediate-risk AML who did not present with *NPM1*, *CEBPA*, or *FLT3* internal tandem duplication (ITD) variants.[16] During the initial analysis (donor vs no-donor), RFS rates were better for patients who had an available sibling donor (n=83) than for those who lacked a matched sibling donor (49% vs 26%; HR=0.5; 95% CI, 0.3 to 0.9; p=0.02); a similar improvement was seen for OS, although not statistically significant (p=0.08). The authors also conducted a time-dependent multivariate analysis to account for the significantly longer time-from-CR1 observed in patients treated with allo-HCT (median, 115 days) compared with those treated with postremission chemotherapy (median, 78 days; p<0.001). Rates of OS after 5 years were superior for the group who received allo-HCT than for those receiving chemotherapy (OS, 66% vs 46%, respectively; HR=0.58; 95% CI, 0.37 to 0.9; p=0.02), as were rates of RFS (5-year RFS, 55% vs 31%; HR=0.51; 95% CI, 0.34 to 0.76; p=0.001). The investigators acknowledged that 38% of the group assigned to post-remission chemotherapy received allo-HCT following a relapse, which might have contributed to a crossover effect.

In 2017, Canaani et al published a retrospective analysis of 1275 patients who underwent HCT; of these, 918 patients had normal white blood cell (WBC) counts, and the rest presented with abnormally high WBC (hyperleukocytosis).[17] For 159 patients in the latter group, WBC counts were between 50,000 and 100,000/μL; for 198 patients, WBC counts were greater than 100,000. By comparing end points such as relapse incidence, leukemia-free survival, nonrelapse mortality, and the occurrence of acute or chronic graft-versus-host disease (GVHD) between groups, the authors evaluated hyperleukocytosis as a potential prognostic indicator of outcomes following transplantation. At baseline, patients in the intermediate- and high-WBC groups had younger median ages (49.1 years and 48.8 years, respectively) than patients without hyperleukocytosis (median age, 52.2 years); additionally, patients with high WBC were associated with the presence of *FLT3*-ITD and *NPM1* variants (p<0.001), and there were significant differences between

groups regarding cytogenetic risk category (p<0.001) and the choice of conditioning regimen, whether myeloablative or reduced-intensity (p=0.02). In multivariate analysis, patients with hyperleukocityosis (intermediate and high WBC) were more likely to experience relapse than patients with less than 50,000/μL WBC (29% and 30% vs 22%, respectively); the HR was 1.55 (95% CI, 1.14 to 2.12; p=0.004). Negative outcomes were again linked to patients with hyperleukocytosis for leukemia-free survival and OS, which were favorable for non-hyperleukocytosis patients (respective HRs were as follows: 1.38 [95% CI, 1.07 to 1.78], p=0.013; and 1.4 [95% CI, 1.07 to 1.87], p=0.013). Such findings were statistically significant when different types of transplantation sources (a matched sibling vs an unrelated donor) were accounted for, leading investigators to recommend the use of hyperleukocytosis as a predictor of clinical outcomes following allogeneic HCT.

Section Summary: Allo-HCT for Chemotherapy-Responsive Consolidation
Evidence for the use of allo-HCT for patients with AML in CR1 consists RCTs and matched cohort studies. Some studies have compared allo-HCT with autologous HCT or with postremission chemotherapy. OS rates and DFS rates were favorable for allo-HCT compared with conventional chemotherapy. In a paired comparison with patients receiving chemotherapy, patients receiving allo-HCT experienced significantly higher RFS rates. Two retrospective studies analyzed subgroups of allo-HCT patients who did not present with several common genetic variants or who presented with hyperleukocytosis. Survival rates appear to be associated with the presence of MRD and cytogenetic prognosis group.

Allo-HCT for AML Refractory to Chemotherapy
Conventional dose induction chemotherapy will not produce remission in 20% to 40% of patients with AML, connoting refractory AML.[6] An allo-HCT using a matched related donor or matched unrelated donor represents the only potentially curative option for these patients. In several retrospective studies, OS rates have ranged from 30% at 3 years to 13% at 5 years, although this procedure is accompanied by nonrelapse mortality rates of 25% to 62% in this setting.[7] For patients who lack a suitable donor (matched related donor or matched unrelated donor), alternative treatments include salvage chemotherapy with high-dose cytarabine or etoposide-based regimens, monoclonal antibodies (eg, gemtuzumab ozogamicin), multidrug resistance modulators, and investigational agents (eg, *FLT3* antagonists).[18] Because it is likely that stem cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, upfront autologous HCT has no role in patients who fail induction therapy.[19]

Section Summary: Allo-HCT for AML Refractory to Chemotherapy
Evidence for the use of allo-HCT for individuals with primary AML refractory to chemotherapy consists of retrospective studies compiled from data from phase 3 trials and registries. OS rate estimates are 30% at 3 years and 13% at 5 years; however, the procedure is accompanied by high rates of nonrelapse mortality (estimated range, 25%-62%). Nonetheless, these results may provide clinically meaningful benefit for such patients who do not have other treatment options. Autologous HCT is not recommended for patients who have failed induction

therapy, because malignant cells may be included in the stem cell preparation process.

Allo- or Autologous HCT for Relapsed AML After Chemotherapy
Most patients with AML will experience disease relapse after attaining a CR1.[6] Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved.

A 2005 study by Breems et al evaluated retrospective data from 667 patients who had relapsed, among a total of 1540 patients entered in 3 phase 3 trials who had received HCT during CR1. The analysis suggested that use of allo-HCT among relapsed patients can produce 5-year OS rates of 26% to 88%, depending on cytogenetic risk stratification.[20] Because reinduction chemotherapy may be associated with substantial morbidity and mortality, patients whose disease has relapsed and who have a suitable donor may proceed directly to allo-HCT.

In patients without an allogeneic donor or who are not candidates for allo-HCT due to age or other factors, autologous HCT may achieve prolonged DFS in 9% to 55% of patients in CR2 depending on risk category.[19,21] 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 HCT in this setting is usually limited to patients who have a sufficient stem cell preparation remaining from collection in CR1.[19]

Allo-HCT is often performed as salvage therapy for patients who have relapsed after conventional chemotherapy or autologous HCT.[19] The decision to attempt reinduction or proceed directly to allo-HCT 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 have shown DFS rates of 44% using sibling allografts and 30% with matched unrelated donor allografts at 5 years for patients transplanted in CR2, and DFS rates of 35% to 40% using sibling transplants and 10% with matched unrelated donor transplants for patients with induction failure or in relapse following HCT.[19]

In a 2017 retrospective chart review, Frazer et al assessed characteristics that might predict OS, relapse rate, and nonrelapse mortality of HCT in patients with relapsed AML.[22] Data were abstracted from 55 consecutive patients who underwent allo-HCT for AML in CR2. OS rates at 1, 3, and 5 years posttransplant were 60%, 45%, and 37%, respectively. None of the following pretransplant variables was significantly associated with OS, relapse rate, or nonrelapse mortality: duration of first remission, patient age, cytogenetic risk category, post myelodysplastic syndrome, conditioning regimen, or donor type. Limitations of the study were its small sample size and selection parameters that included transplantations conducted across 21 years.

Section Summary: Allo- or Autologous HCT for Relapsed AML After Chemotherapy

Evidence on the use of HCT for individuals with relapsed AML includes retrospective chart reviews compiling data from phase 3 trials and registries. DFS rates ranged from 30% to 44% depending on the source of transplantation cells, and OS rates ranged from 26% to 88% depending on risk stratification. Because reinduction chemotherapy may be associated with high morbidity and mortality, HCT may be considered.

Allo-HCT with RIC

A body of evidence is accruing from clinical studies that RIC with allo-HCT may be used for consolidation therapy in patients with AML.[23-35]

Systematic Reviews

A 2016 systematic review and meta-analysis by Rashidi et al calculated OS and RFS for patients older than 60 years of age with AML who underwent RIC HCT.[36] A literature search, conducted through September 2015, identified 13 studies (total N=749 patients) for inclusion. Pooled estimates for RFS at 6 months, 1 year, 2 years, and 3 years were 62% (95% CI, 54% to 69%), 47% (95% CI, 42% to 53%), 44% (95% CI, 33% to 55%), and 35% (95% CI, 26% to 45%), respectively. Pooled estimates for OS at 6 months, 1 year, 2 years, and 3 years were 73% (95% CI, 66% to 79%), 58% (95% CI, 50% to 65%), 45% (95% CI, 35% to 54%), and 38% (95% CI, 29% to 48%), respectively.

A 2014 meta-analysis compared RIC with myeloablative conditioning (MAC) regimens for allo-HCT in patients with AML.[37] The analysis included 23 clinical trials reported between 1990 and 2013, with approximately 15,000 adults. Eleven studies included AML and myelodysplastic syndrome, and five included AML only. A subanalysis from 13 trials in patients with AML or myelodysplastic syndrome revealed that OS was comparable in patients who received either RIC or MAC transplants, and the 2-year or less and 2-year or greater OS rates were equivalent between both conditioning groups. The 2- to 6-year progression-free survival, nonrelapse mortality, and acute and chronic (GVHD rates were reduced after RIC HCT, but relapse rate was increased. Similar outcomes were observed regardless of disease status at transplantation. Among the RIC HCT recipients, survival rates were superior if patients were in complete remission at transplantation.

Randomized Controlled Trials

A randomized comparative trial in matched patient groups compared the net health benefit of allo-HCT with RIC or with MAC.[38-40] In this phase 3 trial, patients (18-60 years) were randomized to 4 doses of RIC (n=99) at 2 gray of total body irradiation plus fludarabine 150 mg/m^2, or to 6 doses of standard conditioning (n=96) at 2 gray 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 nonrelapse mortality analyzed in the intention-to-treat population. This unblinded trial was stopped early because of slow accrual of patients. The incidence of nonrelapse mortality 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. The DFS rates at 3 years were 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. The OS rates at 3 years were 61% (95% CI, 50% to 74%) in the RIC group and 58% (95% CI, 47% to 70%; HR=0.77; 95% CI, 0.48 to 1.25) in the standard conditioning group. No outcomes differed significantly between groups. Grade 3 and 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 events such as GVHD and increased concentrations of bilirubin and creatinine did not differ significantly between groups.

A phase 2 single-center, randomized toxicity study (2013) compared MAC with RIC in patients who received allo-HCT to treat AML.[41] Adults 60 years of age or younger with AML were randomized (1:1) to treatment with RIC (n=18) or MAC (n=19) for allo-HCT. 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 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 rate of 73% compared with 90% among those in the RIC group.

Comparative Trials

In a 2016 comparative study by the European Society for Blood and Marrow Transplantation, long-term survival was evaluated among patients with AML who underwent allo-HCT with RIC or with MAC regimens.[42] Data from 701 patients receiving MAC and 722 patients receiving RIC were analyzed. Survival, relapse, and GVHD rates are summarized in Table 1. In a multivariate analysis, the following factors predicted nonrelapse mortality: RIC, age older than 55 years, advanced disease, and female donor to male recipient. Factors predicting chronic GVHD (a surrogate outcome for quality of life) were: in vivo T-cell depletion, advanced disease, and peripheral blood cell transplantation.

Table 1. Comparison of 10-Year Outcomes for RIC and MAC Regimens in Patients Undergoing Allo-HCT

Outcomes	RIC (n=722) Rate (95% CI), %	MAC (n=701) Rate (95% CI), %	p
Nonrelapse mortality	20 (17 to 24)	35 (31 to 39)	<0.001

Relapse	48 (44 to 52)	34 (31 to 38)	<0.001
Leukemia-free survival, overall	32 (28 to 35)	31 (27 to 35)	0.57
Age 50-55 y	40 (33 to 46)	36 (32 to 41)	0.32
Age >55 y	20 (14 to 26)	28 (24 to 32)	0.02
Overall survival	35 (32 to 39)	33 (29 to 37)	0.57
GVHD-free, relapse-free survival	21 (18 to 24)	22 (18 to 25)	0.79

Adapted from Shimoni et al (2016).[42]
allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; GVHD: graft-versus-host disease; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning.

In a comparative study by Bitan et al (2014), outcomes were compared for children with AML who underwent allo-HCT using RIC regimens or MAC regimens.[43] A total of 180 patients were evaluated; 39 underwent RIC and 141 received MAC 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 MAC regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were similar for RIC (39%) and MAC regimens (39%; p=0.95), and recipients of MAC regimens were not at a higher risk for transplant-related mortality (16%) than recipients of RIC regimens (16%; p=0.73).

Noncomparative Studies
In a 2015 phase 2 study by Devine et al, 114 patients ages 60 to 74 years with AML in CR1 were treated with RIC and allo-HCT.[44] Patients were followed for 2 years. The primary end point was DFS, and secondary end points were nonrelapse mortality, GVHD, relapse, and OS. Two years after transplantation, the following rates were recorded: DFS, 42% (95% CI, 33% to 52%); OS, 48% (95% CI, 39% to 58%); nonrelapse mortality, 15% (95% CI, 8% to 21%); grades 2, 3, or 4 acute GVHD, 10% (95% CI, 4% to 15%); grades 2, 3, or 4 chronic GVHD, 28% (95% CI, 19% to 36%); and cumulative incidence of relapse, 44% (95% CI, 35% to 53%).

Section Summary: Allo-HCT With RIC
Evidence for the use of RIC and allo-HCT to treat patients with AML consists of 2 RCTs, 2 meta-analyses, and numerous comparative and noncomparative studies. In general, compared with MAC, RIC has comparable survival estimates (leukemia-free, overall), though relapse rates appear higher among patients receiving RIC in some studies.

Autologous HCT for Chemotherapy-Responsive Consolidation

Systematic Reviews
A meta-analysis published in 2004 by Nathan et al compared survival outcomes for autologous HCT in CR1 with standard chemotherapy or no further treatment in AML patients ages 15 to 55 years.[45] Two types of studies were eligible: (1) 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 (2) randomized trials that compared autologous HCT with chemotherapy in all patients. Among a

total of 4058 patients included in 6 studies, 2989 (74%) achieved CR1; 1044 (26%) were randomized to HCT (n=524) or to chemotherapy (n=520). Of the 5 studies for which OS data were available, outcomes with autologous HCT were better in three, and outcomes with chemotherapy were better in two. 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 using autologous HCT compared with chemotherapy (or no further treatment), but only one reported a statistically significant DFS probability associated with autologous HCT. The pooled estimate for DFS showed a statistically significant probability in favor of autologous HCT 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 HCT compared with chemotherapy given the significant estimate for DFS benefit. First, the pooled data showed a 6.45% greater nonrelapse mortality rate in autologous HCT recipients compared with chemotherapy recipients. Second, 14% of chemotherapy recipients whose disease relapsed ultimately achieved a sustained CR2 after undergoing an allogeneic or autologous HCT. The intention-to-treat analysis in the studies, which included the latter cases in the chemotherapy group, might have inappropriately inflated OS rates favoring chemotherapy. Furthermore, this analysis did not take into account the 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 by Wang et al, evaluated autologous HCT plus further chemotherapy or no further treatment for patients with AML in CR1.[46] Nine randomized trials involving 1104 adults who underwent autologous HCT and 1118 patients who received additional chemotherapy or no additional treatment were identified. Analyses suggested that autologous HCT 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 an increased nonrelapse mortality rate (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 HCT than among the chemotherapy recipients or further untreated patients. As a consequence of the increased nonrelapse mortality rate, no statistical difference in OS (HR=1.05; 95% CI, 0.91 to 1.21) was associated with the use of autologous HCT, compared with further chemotherapy or no further therapy. These results are concordant with the earlier meta-analysis.

Randomized Controlled Trials
A prospective, randomized phase 3 trial by Vellenga et al (2011) compared autologous HCT with intensive consolidation chemotherapy among patients (range, 16-60 years) with newly diagnosed AML of similar risk profiles in CR1.[47] After 2

cycles of intensive chemotherapy (etoposide and mitoxantrone), patients in CR1—who were not candidates for allo-HCT—were randomized to a third consolidation cycle of the same chemotherapy (n=259) or autologous HCT (n=258). The HCT group experienced an upward trend toward superior RFS (38%) compared with the chemotherapy group at 5 years (29%; p=0.065). HCT patients also had a lower relapse rate at 5 years (58%) compared with chemotherapy recipients (70%; p=0.02). OS did not differ between the HCT group (44%) and the chemotherapy group (41%; p=0.86). Nonrelapse mortality rates were higher in the autologous HCT group (4%) than in the chemotherapy consolidation group (1%; p=0.02). Despite this difference in nonrelapse mortality, 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-HCT—in the chemotherapy consolidation recipients that were not available to the autologous HCT patients. This large trial has shown an advantage for postremission autologous HCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy-consolidated patients.

Section Summary: Autologous HCT for Chemotherapy-Responsive Consolidation
Evidence for the use of autologous HCT for patients with AML who do not have a suitable allogeneic donor or who cannot tolerate an allogeneic procedure consists of several RCTs comparing autologous HCT with chemotherapy and prospective cohort studies. Meta-analyses of these studies and trials were reported improved DFS and relapse but did not find a significant improvement in OS. A potential explanation for this discrepancy between DFS and OS is the increased nonrelapse mortality rate experienced by patients in the transplantation group.

Summary of Evidence
For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission who receive allo-HCT with MAC, the evidence includes RCTs and matched cohort studies. Relevant outcomes are overall survival and disease-specific survival. 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 an intention-to-treat analysis. Survival rates appear to be associated with the 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 MAC, the evidence 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 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 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 MAC, the evidence 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 has shown that allo-HCT improves overall survival 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 and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning, the evidence includes 2 randomized controlled trials, 2 meta-analyses, and other comparative and noncomparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. The randomized controlled trials compared reduced-intensity conditioning with MAC and reported similar rates in nonrelapse mortality, relapse, and overall survival though one of the trials was stopped prematurely due to a slow accrual of patients. Two retrospective comparative studies found no difference in overall survival or leukemia-free survival between the conditioning regimens. It appears unlikely that additional comparative evidence will 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 first complete remission 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. Relevant outcomes are overall and disease-specific survival. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved disease-free survival rates. Overall survival 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.

Supplemental Information

Clinical Input 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 in 2009. There was a strong consensus among reviewers that allogeneic hematopoietic cell transplantation 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

National Comprehensive Cancer Network
The National Comprehensive Cancer Network clinical guidelines (v.3.2017) for acute myeloid leukemia (AML) are consistent with this review.[48] The Network guidelines state that HCT 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 HCT in first complete remission or considered at first relapse in appropriate patients concomitant with reinduction therapy. Recommendations also include autologous HCT in patients who achieve second molecular remission and to reserve allogeneic transplant for those patients who have persistent disease, despite therapy for relapsed disease.

European Society for Blood and Marrow Transplantation
As part of the position statement published in 2017 on behalf of the European Society for Blood and Marrow Transplantation (EBMT, Lee et al summarized the current literature regarding allogeneic HCT (allo-HCT) in patients with AML.[49] For patients who lack a matched related or unrelated donor, recent retrospective and registry studies have suggested that allogeneic HCT is an option using a donor who is haploidentical to the patient or in whom all but 1 or 2 human leukocyte antigen loci match that of the patient. While the EBMT did not determine a superior method for haploidentical HCT, it was noted that the preliminary evidence suggests patient outcomes similar to those observed following single or double umbilical cord blood transplantation. The review of the literature did not include pooled analyses of the results, but the EBMT advocates that more prospective studies be conducted, given the potential benefit for AML patients who do not have eligible donors under standard guidelines.

Canadian Consensus Guidelines
Brandwein et al (2017) updated evidence-based consensus guidelines from a group of Canadian leukemia experts on the appropriate induction regimens for AML patients who are older; the group considered both candidates for allo-HCT and patients ineligible for transplant.[50] The consensus group expanded the indication for induction therapy to any patient younger than 80 years old who is eligible for HCT and who does not present with high comorbidities or adverse risk cytogenetics. As potential induction regimens for individuals with intermediate-to-favorable risk cytogenetics, the consensus group recommended the 3+7 regimen

(which may include daunorubicin, idarubicin, or mitoxantrone, followed by cytarabine) or, if unable to receive anthracyclines, the FLAG regimen, which consists of fludarabine, cytarabine, and filgrastim. Midostaurin may be administered to patients younger than 70 years in whom a *FLT3* internal tandem duplication or tyrosine kinase domain variant is detected; if no such variant (*FLT3*) is present, gemtuzumab ozogamicin may be administered. Concerning HCT, the consensus group confirmed that haploidentical donors may be selected for patients who lack a matched donor (whether a relative or unrelated); and HCT may be considered in patients younger than 75 years of age and in patients whose disease is in second complete remission.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services have the following national coverage determination on use of autologous cell transplantation for AML[51]: "Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched."

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00342316	Prospective Controlled Clinical Study of Allogeneic Stem Cell Transplantation with Reduced Conditioning versus Best Standard Care in Acute Myeloid Leukemia in First Complete Remission	360	Dec 2017
NCT02626715	A Phase II Study of Myeloablative and Reduced-Intensity Conditioning Regimens for Children with Acute Myeloid Leukemia or Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Stem Cell Transplantation	16	Sep 2019
NCT02441803	Allogeneic Hematopoietic Stem Cell Transplantation as Initial Salvage Therapy for Patients with Primary Induction Failure Acute Myeloid Leukemia Refractory to High-Dose Cytarabine-Based Induction Chemotherapy	75	Sep 2022
Unpublished			
NCT00766779	Randomized Phase III Study Comparing Conventional Chemotherapy to Low Dose Total Body Irradiation-Based Conditioning and HCT from Related and Unrelated Donors as Consolidation Therapy for Older Patients with AML in 1st Complete Remission	231	Dec 2018 (terminated)

NCT: national clinical trial.

References
1. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML). n.d.; https://seer.cancer.gov/statfacts/html/amyl.html. Accessed January 8, 2018.
2. Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. Sep 17 2015;373(12):1136-1152. PMID 26376137
3. Li D, Wang L, Zhu H, et al. Efficacy of allogeneic hematopoietic stem cell transplantation in intermediate-risk acute myeloid leukemia adult patients in first complete remission: a meta-analysis of prospective studies. PLoS One. Jul 21 2015;10(7):e0132620. PMID 26197471
4. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. Jun 10 2009;301(22):2349-2361. PMID 19509382
5. Yanada M, Matsuo K, Emi N, et al. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. Cancer. Apr 15 2005;103(8):1652-1658. PMID 15742336
6. Baer MR, Greer JP. Acute myeloid leukemia in adults. In: Greer JP, Foerser J, Rodgers GM, et al., eds. Wintrobe's Clinical Hematology (12th ed.). Vol 2. Philadelphia: Lippincott Williams & Wilkins; 2009:1843-1888.
7. Hamadani M, Awan FT, Copelan EA. Hematopoietic stem cell transplantation in adults with acute myeloid leukemia. Biol Blood Marrow Transplant. May 2008;14(5):556-567. PMID 18410898
8. Deschler B, de Witte T, Mertelsmann R, et al. Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches. Haematologica. Nov 2006;91(11):1513-1522. PMID 17082009
9. Craddock CF. Full-intensity and reduced-intensity allogeneic stem cell transplantation in AML. Bone Marrow Transplant. Mar 2008;41(5):415-423. PMID 18209726
10. Cornelissen JJ, van Putten WL, Verdonck LF, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood. May 1 2007;109(9):3658-3666. PMID 17213292
11. Mrózek K, Bloomfield CD. Chromosome aberrations, gene mutations and expression changes, and prognosis in adult acute myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2006:169-177. PMID 17124057
12. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. J Clin Oncol. Aug 20 2006;24(24):3904-3911. PMID 16921041
13. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. May 1 2008;358(18):1909-1918. PMID 18450602
14. Buckley SA, Wood BL, Othus M, et al. Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis. Haematologica. May 2017;102(5):865-873. PMID 28126965
15. Stelljes M, Krug U, Beelen DW, et al. Allogeneic transplantation versus chemotherapy as postremission therapy for acute myeloid leukemia: a prospective matched pairs analysis. J Clin Oncol. Feb 1 2014;32(4):288-296. PMID 24366930
16. Heidrich K, Thiede C, Schafer-Eckart K, et al. Allogeneic hematopoietic cell transplantation in intermediate risk acute myeloid leukemia negative for FLT3-ITD, NPM1- or biallelic CEBPA mutations. Ann Oncol. Nov 1 2017;28(11):2793-2798. PMID 28945881
17. Canaani J, Labopin M, Socie G, et al. Long term impact of hyperleukocytosis in newly diagnosed acute myeloid leukemia patients undergoing allogeneic stem cell transplantation: An analysis from the acute leukemia working party of the EBMT. Am J Hematol. Jul 2017;92(7):653-659. PMID 28370339
18. Estey EH. Treatment of acute myeloid leukemia. Haematologica. Jan 2009;94(1):10-16. PMID 19118375
19. Stone RM, O'Donnell MR, Sekeres MA. Acute myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2004:98-117. PMID 15561679

20. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol. Mar 20 2005;23(9):1969-1978. PMID 15632409

21. Breems DA, Lowenberg B. Acute myeloid leukemia and the position of autologous stem cell transplantation. Semin Hematol. Oct 2007;44(4):259-266. PMID 17961725

22. Frazer J, Couban S, Doucette S, et al. Characteristics predicting outcomes of allogeneic stem-cell transplantation in relapsed acute myelogenous leukemia. Curr Oncol. Apr 2017;24(2):e123-e130. PMID 28490935

23. Hamadani M, Mohty M, Kharfan-Dabaja MA. Reduced-intensity conditioning allogeneic hematopoietic cell transplantation in adults with acute myeloid leukemia. Cancer Control. Oct 2011;18(4):237-245. PMID 21976242

24. Oliansky DM, Appelbaum F, Cassileth PA, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults: an evidence-based review. Biol Blood Marrow Transplant. Feb 2008;14(2):137-180. PMID 18215777

25. Blaise D, Vey N, Faucher C, et al. Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. Haematologica. Apr 2007;92(4):533-541. PMID 17488664

26. Huisman C, Meijer E, Petersen EJ, et al. Hematopoietic stem cell transplantation after reduced intensity conditioning in acute myelogenous leukemia patients older than 40 years. Biol Blood Marrow Transplant. Feb 2008;14(2):181-186. PMID 18215778

27. Valcarcel D, Martino R. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in myelodysplastic syndromes and acute myelogenous leukemia. Curr Opin Oncol. Nov 2007;19(6):660-666. PMID 17906468

28. Valcarcel D, Martino R, Caballero D, et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. J Clin Oncol. Feb 1 2008;26(4):577-584. PMID 18086801

29. Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. J Clin Oncol. Jun 10 2010;28(17):2859-2867. PMID 20439626

30. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. Apr 10 2010;28(11):1878-1887. PMID 20212255

31. Peffault de Latour R, Porcher R, Dalle JH, et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. Blood. Dec 19 2013;122(26):4279-4286. PMID 24144640

32. Hamidieh AA, Alimoghaddam K, Jahani M, et al. Non-TBI hematopoietic stem cell transplantation in pediatric AML patients: a single-center experience. J Pediatr Hematol Oncol. Aug 2013;35(6):e239-245. PMID 23042019

33. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. Jan 20 2010;28(3):405-411. PMID 20008642

34. Peffault de Latour R, Porcher R, Dalle JH, et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. Blood. Dec 19 2013;122(26):4279-4286. PMID 24144640

35. Pemmaraju N, Tanaka MF, Ravandi F, et al. Outcomes in patients with relapsed or refractory acute promyelocytic leukemia treated with or without autologous or allogeneic hematopoietic stem cell transplantation. Clin Lymphoma Myeloma Leuk. Aug 2013;13(4):485-492. PMID 23769669

36. Rashidi A, Ebadi M, Colditz GA, et al. Outcomes of allogeneic stem cell transplantation in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis. Biol Blood Marrow Transplant. Apr 2016;22(4):651-657. PMID 26529178

37. Abdul Wahid SF, Ismail NA, Mohd-Idris MR, et al. Comparison of reduced-intensity and myeloablative conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and acute lymphoblastic leukemia: a meta-analysis. Stem Cells Dev. Nov 01 2014;23(21):2535-2552. PMID 25072307

38. Bornhauser M, Kienast J, Trenschel R, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. Lancet Oncol. Oct 2012;13(10):1035-1044. PMID 22959335

39. Scherwath A, Schirmer L, Kruse M, et al. Cognitive functioning in allogeneic hematopoietic stem cell transplantation recipients and its medical correlates: a prospective multicenter study. Psychooncology. Jul 2013;22(7):1509-1516. PMID 22945857

40. Shayegi N, Kramer M, Bornhauser M, et al. The level of residual disease based on mutant NPM1 is an independent prognostic factor for relapse and survival in AML. Blood. Jul 04 2013;122(1):83-92. PMID 23656730

41. Ringden O, Erkers T, Aschan J, et al. A prospective randomized toxicity study to compare reduced-intensity and myeloablative conditioning in patients with myeloid leukaemia undergoing allogeneic haematopoietic stem cell transplantation. J Intern Med. Aug 2013;274(2):153-162. PMID 23432209

42. Shimoni A, Labopin M, Savani B, et al. Long-term survival and late events after allogeneic stem cell transplantation from HLA-matched siblings for acute myeloid leukemia with myeloablative compared to reduced-intensity conditioning: a report on behalf of the acute leukemia working party of European Group for Blood and Marrow Transplantation. J Hematol Oncol. Nov 08 2016;9(1):118. PMID 27821187

43. Bitan M, He W, Zhang MJ, et al. Transplantation for children with acute myeloid leukemia: a comparison of outcomes with reduced intensity and myeloablative regimens. Blood. Mar 6 2014;123(10):1615-1620. PMID 24435046

44. Devine SM, Owzar K, Blum W, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. J Clin Oncol. Dec 10 2015;33(35):4167-4175. PMID 26527780

45. Nathan PC, Sung L, Crump M, et al. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. J Natl Cancer Inst. Jan 07 2004;96(1):38-45. PMID 14709737

46. Wang J, Ouyang J, Zhou R, et al. Autologous hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission: a meta-analysis of randomized trials. Acta Haematol. Jul 2010;124(2):61-71. PMID 20616541

47. Vellenga E, van Putten W, Ossenkoppele GJ, et al. Autologous peripheral blood stem cell transplantation for acute myeloid leukemia. Blood. Dec 1 2011;118(23):6037-6042. PMID 21951683

48. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Acute myeloid leukemia. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed December 21, 2017.

49. Lee CJ, Savani BN, Mohty M, et al. Haploidentical hematopoietic cell transplantation for adult acute myeloid leukemia: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. Nov 2017;102(11):1810-1822. PMID 28883081

50. Brandwein JM, Zhu N, Kumar R, et al. Treatment of older patients with acute myeloid leukemia (AML): revised Canadian consensus guidelines. Am J Blood Res. Jul 2017;7(4):30-40. PMID 28804680

51. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&DocID=110.23&list_type=ncd&bc=gAAAAAgAAAAAA%3d%3d&. Accessed December 22, 2017.

Billing Coding/Physician Documentation Information

0050U   Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements

0056U	Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s)
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38220	Bone marrow; aspiration only
38221	Bone marrow; biopsy, needle or trocar
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogenic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
J9000–J9999	Chemotherapy drug code range.
Q0083	Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit
Q0084	Chemotherapy administration by infusion technique only, per visit
Q0085	Chemotherapy administration by both infusion technique and other technique(s) (eg, subcutaneous, intramuscular, push), per visit
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	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 services; and the number of days of pre- and post transplant care in the global definition

ICD-10 Codes

C92.00- Acute myeloblastic leukemia code range
C92.02
C92.40- Acute promyelocytic leukemia code range
C92.42
C92.50- Acute myelomonocytic leukemia code range
C92.52

Additional Policy Key Words

Genetic Testing
Stem Cell

Policy Implementation/Update Information

7/1/02	New policy added to the Medical section.
8/1/03	No policy statement changes.
7/1/04	No policy statement changes. Changed from Medical section to Surgery and Transplant sections.
7/1/05	No policy statement changes.
4/1/06	Considerations section revised to include general criteria.
7/1/06	No policy statement changes.
7/1/07	No policy statement changes.
7/1/08	No policy statement changes.
2/12/09	Interim update. Policy statement changed to indicate that, Reduced-intensity conditioning allogeneic SCT may be considered medically necessary as a treatment of AML in patients who are in complete marrow and extramedullary first or second remission, and who for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Title changed from High Dose Chemotherapy with Hematopoietic Stem Cell Support for Acute Myelogenous Leukemia to Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
7/1/09	No policy statement changes.
7/1/10	Policy statements revised indicating that allogeneic HSCT may be used in those with poor- to intermediate-risk AML in remission and that allogeneic HSCT may be used after failed autologous HSCT.
7/1/11	No policy statement changes.
1/1/12	Coding updated.
7/1/12	No policy statement changes.
10/1/12	No policy statement changes.
10/1/13	No policy statement changes.
10/1/14	Updated CPT codes. No policy statement changes.
10/1/15	Policy statements updated with clarifying information and to align with

other HSCT policies but the intent remains unchanged.

10/1/16 No policy statement changes.

10/1/17 "Stem" removed from title and policy. HSCT changed to HCT in Policy and Policy Guidelines. Policy statements otherwise unchanged.

10/1/18 No policy statement changes.