Medical Policy

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Title: BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Description/Background

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

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a disorder of immature dendritic cells that regulate effector T-cell function.(2) It constitutes only 0.44% of hematologic malignancies and <1% of acute leukemia presentations. It most commonly presents as asymptomatic skin lesions, cytopenias, circulating peripheral blasts (leukemic phase), lymphadenopathy, and CNS manifestations. Prognosis for BPDCN is poor and the median overall survival (OS) is approximately 8–12 months when patients are treated with chemotherapy. Studies suggest that being in first remission (CR1) during receipt of allogeneic HCT significantly enhances the median OS.

Acute Myeloid Leukemia Treatment

Complete remission of acute myeloid leukemia (AML) 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 post remission (consolidation) strategies, typically using high-dose chemotherapy with autologous HCT or high-dose or reduced-intensity chemotherapy with allo-HCT. The two treatments, autologous HCT and allo-HCT—represent two different strategies. The first, autologous HCT, is a “rescue,” but not a therapeutic procedure; the second, allo-HCT, is a “rescue” plus a therapeutic procedure.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that is mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by extant disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allo-HCT

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

regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

A 2015 review in the *New England Journal of Medicine* has summarized advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments.(1) The National Comprehensive Cancer Network guidelines provide updated information on genetic markers for risk stratification, and additional recent reviews summarize information on novel therapies for AML.(2,3,4)

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.

Medical Policy Statement

The safety and effectiveness of hematopoietic cell transplantation for acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasm (BPDCN) have been established. It may be considered a useful therapeutic option for individuals meeting specified guidelines.

Inclusionary and Exclusionary Guidelines

Inclusions:

- **Allogeneic** hematopoietic cell transplantation (HCT) using a **myeloablative** conditioning regimen for individuals with **one** of the following:
  - Poor- to intermediate-risk AML in first complete remission (CR1) (see Policy Guidelines for information on risk stratification)**.**
  - AML that is refractory to standard induction chemotherapy but can be brought into CR with intensified chemotherapy; (NOTE: primary refractory acute myeloid leukemia [AML] is defined as leukemia that does not achieve a complete remission after conventionally dosed [non-marrow ablative] chemotherapy)**.**
  - AML that relapses following chemotherapy-induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy**.**
  - AML in individuals 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.
  - AML in individuals who have relapsed more than 6 months post allogeneic hematopoietic cell transplantation.
  - AML in individual when the first allogeneic hematopoietic cell transplantation was unsuccessful due to primary graft failure.

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) following first complete remission CR1.

- **Allogeneic** hematopoietic cell transplantation (HCT) using a **reduced-intensity** conditioning regimen in individuals with **one** of the following:
  - AML 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 section).
  - AML in individuals who have relapsed more than 6 months post allogeneic hematopoietic cell transplantation.
  - AML in individual when the first allogeneic hematopoietic cell transplantation was unsuccessful due to primary graft failure.
  - BPDCN - reduced intensity conditioning may be considered in individuals who achieve CR but cannot tolerate myeloablative transplantation.

- **Autologous** hematopoietic stem-cell transplantation (HCT) in individuals with **one** of the following:
  - AML in CR1 or beyond.
  - Relapsed AML if responsive to intensified induction chemotherapy.

Exclusions:
- All other indications not specified under the inclusions.

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 inter-relates morphology, cytogenetics, molecular genetics and immunologic markers. It attempts to construct a classification that is universally applicable and prognostically valid. The WHO system was adapted by the National Comprehensive Cancer Network to estimate individual prognosis to guide management, as shown in Table PG1.

Table PG1. Risk Status of Acute Myeloid Leukemia Based on Genetic Factors

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *RUNX1* (if not co-occurring with favorable-risk AML subtypes) Mutated *ASXL1* (if not co-occurring with favorable-risk AML subtypes) Mutated *TP53*

AML: acute myeloid leukemia. This criteria does not apply to BPDCN.

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

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HSCT. These include patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient whose disease relapses following a conventional myeloablative allogeneic HSCT could undergo a second myeloablative procedure if a suitable donor is available and the patient's medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HSCT if a complete remission could be re-induced with chemotherapy.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, -B, and DR (antigen-D related) 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 individual, for which there usually is sharing of only three of the six major histocompatibility antigens. Most individuals 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.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38206	38207	38208	38209
38210	38211	38212	38213	38214	38215
38230	38232	38240	38241	38242	38243

81267	81268	81370	81371	81372	81373
81374	81375	81376	81377	81378	81379
81380	81381	81382	81383	86812	86813
86816	86817	86821	S2140	S2142	S2150

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Potential Contraindications For Transplant:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipient and have decided to proceed.

Rationale

Allogeneic Hematopoietic Stem Cell Transplant with Myeloablative Conditioning for Cytogenic or Molecular Intermediate- or Poor-Risk Acute Myeloid Leukemia in Complete Remission

Clinical Context and Therapy Purpose

The purpose of allogeneic (allo-) hematopoietic cell transplantation (HCT) with myeloablative conditioning (MAC) in individuals who have cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia(AML) in first complete remission (CR1) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with cytogenetic or molecular intermediate- or poor-risk AML in CR1.

Interventions
The therapy being considered is allo-HCT with myeloablative conditioning.

Comparators
The following therapies are currently being used to make decisions about cytogenetic or molecular intermediate- or poor-risk AML inCR1: conventional chemotherapy.

Outcomes
The general outcomes of interest are survival outcomes (overall survival [OS], disease-specific survival [DSS] and disease-free survival [DFS]), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in patients with chemotherapy but without HCT is approximately 20 months.(2) Individuals are followed up throughout their lifespan.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
Masetti et al (2022) conducted a meta-analysis of allo-HCT for pediatric patients with AML in CR1.(56) Both prospective and retrospective studies comparing allo-HCT to chemotherapy in higher-risk patients were considered. A total of 9 studies (5 prospective, 4 retrospective) were included; none of the prospective studies were randomized. The meta-analysis showed that OS was improved with allo-HCT compared with chemotherapy (risk ratio, 1.15; 95% confidence interval [CI], 1.06 to 1.24; I2=0%). Similarly, DFS was improved with allo-HCT compared to chemotherapy (risk ratio, 1.31; 95% CI, 1.17 to 1.47; I2=1%). Risk of relapse was higher among patients who received chemotherapy (risk ratio, 1.26; 95% CI, 1.07 to 1.49; I2=23%).

A 2015 meta-analysis examined prospective trials of adult patients with intermediate risk AML in first complete remission (CR1) who underwent HCT.(6) The analysis included 9 prospective, controlled studies that enrolled a total of 1950 patients between the years 1987 and 2011 (sample range, 32-713 patients).In this analysis, allogeneic HCT was associated with significantly better relapse-free survival (RFS), overall survival (OS), and relapse rate (RR) 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 (TRM) was significantly higher following allogeneic 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 allogeneic HCT over autologous HCT (HR=0.99; 95% CI, 0.70 to 1.39).

A 2009 meta-analysis incorporated data from 24 trials involving 6007 patients who underwent allo-HCT in CR1.(7) 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 hazard ratio for OS among poor-risk patients across 14 trials was 0.73 (95% CI, 0.59 to 0.90; p<.01); among intermediate-risk patients across 14 trials, the hazard ratio for OS was 0.83 (95% CI, 0.74 to 0.93; p<.01); and among good-risk patients across 16 trials, the hazard ratio for OS was 1.07 (95% CI, 0.83 to 1.38; p=.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 are in line with those from another meta-analysis (8) 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 five studies (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 disease-free survival (DFS) as outcomes of interest. This analysis showed a significant advantage of allo-HCT regarding OS for the entire cohort (fixed-effects model HR=1.17; 95% CI, 1.06 to 1.30; p=.003; random-effects model HR=1.15; 95% CI, 1.01 to 1.32; p=.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 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 (e.g., SWOG, Medical Research Council, European Organisation for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell' Adulto).(9) 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.(10-13)

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 non-relapse mortality. However, there is considerable genotypic heterogeneity within the three World Health Organization cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics.(14) For example, patients with better-prognosis disease (e.g., core-binding factor AML) based on cytogenetics, and a variant in the *KIT* gene of leukemic blast cells, do just as poorly with post-remission standard chemotherapy as patients with cytogenetically poor-risk AML.(15) 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, is a gene that encodes FMS-like receptor tyrosine kinase three, a growth factor active in hematopoiesis). Thus, patients with variants in NPM1 but without FLT3 internal tandem duplications have post-remission 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.(16) 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 time of HCT and post-transplantation outcomes.(17) The literature search, conducted through June 2016, identified 19 studies (N=1431) 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, 9 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 report that the presence of MRD at 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

Bornhäuser et al (2023) conducted an open-label, 2-arm, multicenter RCT in Germany to assess the ideal post-remission strategy in intermediate-risk AML in CR1.(62) Adults with AML (age 18 to 60 years) in CR1 or CR with incomplete blood cell count recovery after conventional induction therapy who had availability of a human leukocyte antigen-matched sibling or unrelated donor were included and randomized 1:1 to receive allo-HCT or high-dose cytarabine (HiDAC) for consolidation and salvage HCT only in cases of relapse. The primary outcome was OS, DFS, incidence of relapse, treatment-related mortality, and quality of life measures according to the Medical Outcomes Study 36-Item Short-Form Health Survey were secondary outcomes. One hundred forty-three patients (mean age, 48.2 years, standard deviation, 9.8 years; 57% male) with AML were randomized. At 2 years, the probability of survival was 74% (95% CI, 62% to 83%) after primary allo-HCT and 84% (95% CI, 73% to 92%) after HiDAC (p=.22). Disease-free survival at 2 years was 69% (95% CI, 57% to 80%) after HCT compared with 40% (95% CI, 28% to 53%) after HiDAC (p=.001). The cumulative incidence of relapse at 2 years with allo-HCT was 20% (95% CI, 13% to 31%) compared with 58% (95% CI, 47% to 71%; p<.001) with HiDAC and nonrelapse mortality after allo-HCT was 9% (95% CI, 5% to 19%) versus 2% (95% CI, 0% to 11%) after HiDAC (p=.005). All 41 participants who relapsed after HiDAC proceeded to receive allo-HCT. There were no differences in quality of life measures between groups. Of note, this trial was closed earlier than anticipated due to slow patient accrual, which was a limitation. Additional limitations included the lack of stratification based on MRD and the use of a cytogenetic classifier at trial initiation (2012) which led to inclusion of some favorable-risk patients, which current guidelines would not recommend allo-HCT in CR1. In conclusion, primary allo-HCT during CR1 was not associated with superior OS compared to HiDAC in adults with intermediate-risk AML <60 years, although some secondary endpoints had promising results and were hypothesis generating.

A 2014 study compared outcomes for 185 matched pairs from a large multicenter trial (AMLCG99).(18) Patients younger than 60 years of age who underwent allo-HCT in CR1 were matched to patients who received conventional post-remission chemotherapy. The main matching criteria were AML type, cytogenetic risk group, patient age, and time in CR1. In the overall pair wise-compared AML population, the projected seven-year OS rate was 58% for the

allo-HCT and 46% for the conventional post-remission treatment group (p=.037). The relapse-free survival (RFS) rate was 52% in the allo-HCT group and 33% in the control group (p<.001). The OS was significantly longer for allo-HCT in patient subgroups with non-favorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome (MDS). For the entire patient cohort, post-remission 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.

Retrospective Studies

Heidrich et al (2017) conducted retrospective analyses of subgroups from two 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=.02); a similar improvement was seen for OS, although not statistically significant (p=.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 post-remission chemotherapy (median, 78 days; p<.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=.02), as were rates of RFS (5-year RFS, 55% vs 31%; HR=0.51; 95% CI, 0.34 to 0.76; p=.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.

Section Summary: Allogeneic Hematopoietic Cell Transplant with Myeloablative Conditioning for Cytogenic or Molecular Intermediate- or Poor-Risk AML in Complete Remission

Evidence for the use of allogeneic HCT for patients with AML in first complete remission consists of systematic reviews, RCTs, and matched cohort studies. Some studies compared allogeneic HCT with autologous HCT or with post-remission chemotherapy. In some studies, the overall survival (OS) and disease-free survival (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 relapse-free survival rates. However, in a more recent RCT, there was no difference in OS between allo-HCT and high-dose cytarabine (HiDAC), although there were many limitations associated with this study. 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 presence of minimal residual disease and cytogenetic prognosis group.

ALLOGENEIC HCT WITH MYELOABLATIVE CONDITIONING FOR AML REFRACTORY TO STANDARD INDUCTION CHEMOTHERAPY

Clinical Context and Therapy Purpose

The purpose of allo-HCT with MAC in individuals who have AML refractory to standard induction chemotherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with AML refractory to standard induction chemotherapy.

Interventions
The therapy being considered is allo-HCT with MAC. Allogeneic HCT is an option for AML refractory to standard induction chemotherapy. The purpose is to destroy leukemia cells remaining after induction chemotherapy.

Comparators
The following therapies are currently being used to make decisions about AML refractory to standard induction chemotherapy: conventional chemotherapy.

Outcomes
The general outcomes of interest are survival outcomes (OS and DFS), relapse rates, and treatment-related morbidity. The median survival of patients with AML varies with several known prognostic factors related to patient and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for patients with AML without chemotherapy or HCT is less than 10 months; the median survival in patients with chemotherapy but without HCT is approximately 20 months.(5) Patients are followed up throughout their lifespan.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Review of Evidence

Retrospective Studies
Conventional-dose induction chemotherapy will not produce remission in 20–40% of patients with AML, connoting refractory AML.(9) An allo-HCT 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 30% at 3 years to 13% at 5 years, although this procedure is accompanied by NRM rates of 25–62% in this setting.(10) A 2022 observational study reported higher 3-year and 5-year OS (38% and 33%, respectively), but these rates may lack precision due to a small sample size (N=12).21,Another small study reported 4-year OS of 51.0±10.6% among 29 patients who received allo-HCT and 46.2±9.0% among 34 patients who received salvage chemotherapy followed by allo-HCT, both for refractory AML.(57)

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), (FLT3 antagonists) IDH1/IDH2 inhibitors, and clinical trial enrollment.(2) 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.(20)

Section Summary: Allo-HCT for AML Conditioning for AML Refractory to Standard Induction Chemotherapy
Evidence for the use of allogeneic HCT for individuals with primary AML refractory to chemotherapy consists of retrospective studies compiled from data from phase 3 trials and registries. The overall survival estimates range from 30% to 38% at 3 years and 13% to 51% at 4 to 5 years; however, the procedure is accompanied by high rates of non-relapse mortality (estimates range from 25% to 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.

ALLOGENEIC OR AUTOLOGOUS HCT WITH MYELOABLATIVE CONDITIONING FOR RELAPSED AML AFTER CHEMOTHERAPY-INDUCED REMISSION

Clinical Context and Therapy Purpose
The purpose of allogeneic or autologous HCT with MAC in individuals who have relapsed AML after standard induction chemotherapy-induced CR1 is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with AML who relapsed after standard induction chemotherapy-induced CR1.

Interventions
The therapy being considered is allo-HCT or autologous HCT.

Allogeneic or autologous HCT are options for treatment of relapsed AML after chemotherapy-induced remission. The purpose of HCT is to destroy leukemia cells associated with recurrent AML.

Comparators
The following therapies are currently being used to make decisions about relapsed AML after chemotherapy-induced remission: conventional chemotherapy.

Outcomes
The general outcomes of interest are survival outcomes (OS, DSS and DFS), relapse rates, and treatment related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to patient and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in individuals with chemotherapy but without HCT is approximately 20 months.(5) Individuals are followed up throughout their lifespan.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Review of Evidence

Retrospective Studies

Most patients with AML will experience disease relapse after attaining a CR1.(9) Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved.

A study by Breems et al (2005), evaluated retrospective data from 667 patients who had relapsed, among a total of 1,540 patients entered in three Phase 3 trials who had received HCT during first complete remission. The analysis suggested that use of allo-HCT among relapsed patients can produce five-year OS rates of 26% to 88%, depending on cytogenetic risk stratification.(21) 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.

Allo-HCT is often performed as salvage for patients who have relapsed after conventional chemotherapy or autologous HCT.(20) 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 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 HCT.(20)

In a retrospective chart review, Frazer et al (2017) assessed characteristics that might predict overall survival, relapse rate, and non-relapse mortality of HCT in patients with relapsed AML.(22) Data were abstracted from 55 consecutive patients who underwent allogeneic HCT for AML in CR2. The overall survival rates at 1, 3, and 5 years post-transplant were 60%, 45%, and 37%, respectively. None of the following pre-transplant variables were significantly associated with overall survival, relapse rate, or non-relapse 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.

In patients in CR2 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.(20,23) 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 the collection in CR1.(20)

Section Summary: Allogeneic or Autologous HCT with Myeloablative Conditioning for Relapsed AML After Chemotherapy-Induced Remission

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

ALLOGENEIC HEMATOPOIETIC STEM TRANSPLANT WITH REDUCED-INTENSITY CONDITIONING FOR CYTOGENIC OR MOLECULAR INTERMEDIATE- OR POOR-RISK AML IN REMISSION

Clinical Context and Therapy Purpose
The purpose of allo-HCT with reduced-intensity conditioning (RIC) in individuals who have cytogenetic or molecular intermediate- or poor-risk AML in CR1 who cannot tolerate MAC is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with cytogenetic or molecular intermediate- or poor-risk AML in CR1 who cannot tolerate MAC.

Interventions
The therapy being considered is allo-HCT with reduced-intensity conditioning.

Allogeneic HCT with RIC is an option for post-remission therapy for cytogenic or molecular intermediate- or poor-risk AML. The purpose of post-remission therapy is to destroy undetectable leukemia cells remaining after induction chemotherapy.

Comparators
The following therapies are currently being used to make decisions about cytogenetic or molecular intermediate- or poor-risk AML in CR1: conventional chemotherapy and allo-HCT with MAC.

Outcomes
The general outcomes of interest are survival outcomes (OS, DSS, and DFS), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in patients with chemotherapy but without HCT is approximately 20 months.(5) Patients are followed up throughout their lifespan.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Review of Evidence
A body of evidence is accruing from clinical studies that RIC with allo-HCT may be used for consolidation therapy in patients with AML.(24-35)

Systematic Reviews
Song et al (2021) evaluated the efficacy of RIC followed by allo-HCT in patients with AML and myelodysplastic syndrome via a meta-analysis of 6 RCTs (N=1413).(52) The 6 RCTs compared RIC to MAC before first allo-HCT in patients with AML in complete remission or myelodysplastic syndrome. The primary endpoint was OS. Results revealed that OS was not significantly different between RIC and MAC (HR, 0.95; 95% CI, 0.64 to 1.4; p=.80). The

cumulative incidence of relapse was also similar between the groups (HR, 1.18; 95% CI, 0.88 to 1.49; p=.28). Nonrelapse mortality was significantly improved with RIC as compared to total body irradiation/busulfan-based MAC (HR, 0.53; 95% CI, 0.36 to 0.8; p=.002); however, treosulfan-based MAC significantly reduced nonrelapse mortality as compared to RIC (HR, 1.67; 95% CI, 1.02 to 2.72; p=.04). Reduced-intensity conditioning was associated with a trend of increasing graft failure (p=.06); however, graft failure in both arms was rare. The authors concluded that RIC is recommended as an adequate option of preparative treatment before allo-HCT for patients with AML in complete remission or myelodysplastic syndrome. Limitations of the meta-analysis included the small number of included clinical trials, significant heterogeneity between included studies for some outcomes, and lack of blinding in some studies.

A systematic review and meta-analysis by Rashidi et al (2016) calculated overall survival and relapse-free survival for patients older than 60 years of age with AML who underwent reduced intensity conditioning HCT.(36) A literature search, conducted through September 2015, identified 13 studies (N=749 patients) for inclusion. Pooled estimates for relapse-free survival at six months, one year, two years, and three 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 overall survival at six months, one year, two years, and three 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 reduced-intensity conditioning and 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 adult patients. Eleven studies included AML and myelodysplastic syndrome (MDS) and five included AML only. A subanalysis from 13 trials in patients with AML or MDS showed that OS was comparable in patients who received either RIC or MAC transplants, and the two-year or less and two-year or greater OS rates were equivalent between both conditioning groups. The two- to six-year PFS, non-relapse mortality, and acute and chronic graft-versus-host disease (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 CR at transplantation.

Randomized Controlled Trials

A randomized comparative trial in matched patient groups compared the net health benefit of allo-HCT with RIC versus MAC.(38-40) In this phase 3 trial, patients (18-60 years) were randomized to four doses of RIC (n=99) at two gray of total body irradiation plus fludarabine 150 mg/m^2, or to six doses of standard conditioning (n=96) at two 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 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 three 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 three years were 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 three 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 at three 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 III or IV 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.

A phase 2 single-center, randomized toxicity study (2013) compared MAC with RIC in patients who received allogeneic HCT to treat AML.(38) 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 I was observed in the RIC group compared with grade IV in the MAC group (p<.001). Hemorrhagic cystitis occurred in eight (42%) of the patients in the MAC group and none (0%) in the RIC group (p<.01). Results of renal and hepatic tests did not differ significantly between the groups. The RIC-treated patients had faster platelet engraftment (p<.01) and required fewer erythrocyte and platelet transfusions (p<.001) and less total parenteral nutrition than those treated with MAC (p<.01). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18) (p=.02). Donor chimerism was similar in the two 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 three-year survival of 73% compared with 90% among those in the RIC group.

Comparative Trials

Russell et al (2022) published the results of an observational study of adults aged 60 to 70 years who underwent allo-HCT with RIC compared to patients who received only chemotherapy and did not undergo transplant.(58) A total of 932 patients with AML (not favorable risk) in remission were followed for 60 months, and 144 received allo-HCT with RIC. Five-year OS was 37% among transplant recipients. Allo-HCT with RIC led to improved OS compared to no transplant (37% vs. 20%, respectively; HR, 0.67; 95% CI, 0.53 to 0.84). Relapse-free survival was also improved with allo-HCT with RIC (32% vs. 13%, respectively).

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 allogeneic 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 non-relapse mortality: RIC, age older than 55 years, advanced disease, and female donor to male recipient. Factors predicting chronic GVHD (a surrogate for quality of life) were: in vivo T cell depletion, advanced disease, and peripheral blood stem 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]
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 in children with AML who underwent allo-HCT using RIC or MAC regimens.(43) A total of 180 patients were evaluated; 39 underwent RIC and 141 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 five-year probabilities of OS with RIC and myeloablative regimens were 45% and 48%, respectively (p=.99). Moreover, relapse rates were similar for RIC (39%) and MAC regimens (39%; p=.95), and recipients of MAC regimens were not at a higher risk for transplant-related mortality (16%) than recipients of RIC regimens (16%; p=.73).

Noncomparative Study

In a phase 2 study by Devine et al (2015), 114 patients ages 60 to 74 years with AML in first complete remission were treated with RIC and allogeneic HCT.(41) Patients were followed for 2 years. Primary endpoint was DFS and secondary endpoints were non-relapse mortality, GVHD, relapse, and overall survival. Two years transplantation, the following rates were recorded: disease free survival, 42% (95% CI: 33% to 52%); overall survival, 48% (95% CI: 39% to 58%); non-relapse 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 Reduced-Intensity Conditioning for Cytogenic or Molecular Intermediate- or Poor-Risk AML in Remission

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

ALLOGENEIC HCT FOR PATIENTS WITH BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM FOLLOWING COMPLETE REMISSION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, highly aggressive hematologic malignancy. While the exact incidence is unknown, BPDCN may represent 0.5% of all hematologic malignancies. In 2008, the World Health Organization (WHO) established the term blastic plasmacytoid dendritic cell neoplasm. BPDCN is currently classified by WHO as a distinct entity within the acute myeloid neoplasms and acute leukemias.

Review of Evidence

A study by Lu et al (2022), analyzed data from 15 patients diagnosed with BPDCN who underwent an allo-HCT with myeloablative conditioning (MAC).(53) The male to female ratio was 11:4. The median age of 36 (range: 6–70) years, all patients initially presented with extramedullary lesions (13 with cutaneous lesions, 1 in the breast and 1 in the lymph nodes) and involved the bone marrow, two cases were diagnosed as central nervous system leukemia (CNSL). Nine patients were in first remission (CR1) and six patients were in second remission (CR2) status prior to HCT. All patients received the MAC regimen and an unmanipulated graft. All patients successfully engraftment and achieved full donor chimerism. One patient developed poor graft function, three patients developed acute graft host disease (aGVHD) (Grade I, II, and IV), and seven patients developed chronic graft-versus-host disease (cGVHD) (mild in 6; moderate in 1). The median follow-up time for survival was 34 (range: 6–64) months. The primary endpoint, overall leukemia-free survival (LFS) rate and overall survival

rate was 73.3 ± 10.5%. Allo-HCT with MAC is a valid option for BPDCN patients in complete remission.

HCT should be considered when patients have achieved a complete remission and are sufficiently fit. Long-term remissions have been seen with allo-HCT done during the first remission.(54,55) Relapse following transplantation occurs in approximately 30% of patients.(54) Donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified.(2) Transplantation beyond the first remission or in patients who have not achieved a complete remission appears to have a negative effect on overall survival (OS) and progression-free survival.(54,55) While auto-HCT has been used for consolidation and can improve survival, allo-HCT during the first remission has appeared to offer the best results.(54,55)

AUTOLOGOUS HCT FOR AML IN REMISSION WITH CHEMOTHERAPY-RESPONSIVE CONSOLIDATION

Clinical Context and Therapy Purpose

The purpose of autologous HCT in individuals with AML in remission who do not have a suitable allo-HCT donor is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with AML in remission who do not have a suitable allo-HCT donor.

Interventions

The therapy being considered is autologous HCT. For individuals with AML in remission without an acceptable allo-HCT donor, autologous HCT is an option for consolidation therapy.

Comparators

The following therapies are currently being used to make decisions about the treatment of AML in remission when no suitable allo-HCT donor is available: conventional chemotherapy.

Outcomes

The general outcomes of interest are survival outcomes (OS. DSS, and DFS), relapse rates, and treatment-related morbidity. The median survival of individuals with AML varies with several known prognostic factors related to individual and tumor characteristics such as age, performance status, and karyotype. Overall, the median survival for individuals with AML without chemotherapy or HCT is less than 10 months; the median survival in individuals with chemotherapy but without HCT is approximately 20 months.(3) Individuals are followed up throughout their lifespan.

Study Selection Criteria

Methodologically credible studies were selected using the principles described in the first indication.

Review of Evidence

Systematic Reviews

A meta-analysis by Nathan et al (2004) compared survival outcomes for autologous HCT in CR1 with standard chemotherapy or no further treatment in AML patients ages 15–55 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 4,058 patients included in 6 studies, 2,989 (74%) achieved CR1; 1,044 (26%) were randomized to HCT (n=524) or chemotherapy (n=520). Of the 5 studies for which OS data were available, outcomes with autologous HCT were better in 3, and outcomes with chemotherapy were better in 2. None of the differences were statistical significance, nor was the pooled estimate (fixed-effects model survival probability ratio, 1.01; 95% CI: 0.89-1.15; p=.86). In all 6 studies, DFS was numerically superior with autologous HCT compared with chemotherapy (or no further treatment), but only 1 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 post-transplant (fixed-effects model survival probability ratio=1.24, 95% CI: 1.06-1.44, p=.006). This review 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 by Wang et al (2010), evaluated autologous HCT plus further chemotherapy or no further treatment for patients with AML in CR1.(46) Nine randomized trials involving 1,104 adults who underwent autologous HCT and 1,118 who received additional chemotherapy or no additional treatment were identified. Analyses suggested that autologous HCT in CR1 was associated with statistically significant reduction of relapse risk (RR: 0.56, 95% CI, 0.44 to 0.71, p=.0001) and significant improvement in DFS (HR=0.89, 95% CI, 0.80, 0.98), but at the cost of an increased NRM (RR=1.90, 95% CI, 1.34 to 2.70; p=.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 increased NRM, 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 were concordant with the earlier meta-analysis.

Randomized Controlled Trial

The RCTs published after the meta-analyses will be reviewed here.

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.(44) After two 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 relapse-free survival (38%) compared with the chemotherapy group at five years, p=.065, 95% CI: 0.66, 1.1). The HCT patients also had a lower relapse rate at five years (29%; p=.065). The HCT patients also had a lower relapse rate at 5 years (58%) compared with chemotherapy recipients (70%; p=.02). The overall survival did not differ between HCT group (44%) and the chemotherapy group, (41%; p=.86). NRM were higher in the autologous HCT group (4%) than

in the chemotherapy consolidation group (1%, p=.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-HCT— in the chemotherapy consolidation recipients that were not available to the autologous HCT patients. This large trial has shown an advantage for post-remission autologous HCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy consolidated patients.

Miyamoto et al (2018) reported results of a randomized, multicenter phase 3 trial conducted in 24 centers in Japan from 2003 to 2011 that compared autologous HCT versus high-dose cytarabine (HiDAC) consolidation as post-remission therapy in AML.(48) This trial enrolled 240 patients between 15 and 64 years of age with newly diagnosed favorable- and intermediate-risk AML, Eastern Cooperative Oncology Group performance status of < 3; 87 of those who achieved CR1 were randomized to autologous HCT or HiDAC. The study was powered to include 122 patients with 5 years of accrual and 3 years of post-accrual follow-up to detect a difference in DFS at three years of 40% versus 65%. Approximately one-third of the patients had favorable risk AML and the remaining two-thirds had intermediate-risk AML. The median age was 48 years. Median follow-up was approximately 4.5 to 5 years. Three-year DFS rate was 41% (95% CI, 27% to 55%) in the HiDAC group and 55% (95% CI, 38 %to 68%) in the autologous HCT group (p=.25). Three-year OS was 77% (95% CI, 61% to 87%) versus 68% (95% CI, 52% to 80%) (p=.67). Cumulative incidence of relapse was 54% versus 41% (p=.22). There were no differences between the HiDAC and autologous HCT groups in the incidence of liver or renal dysfunction. The incidence of life-threatening infectious complications (p=.003) and mucositis/diarrhea (p=.002) was significantly higher in the autologous HCT group.

Section Summary: Autologous HCT for AML in Remission with 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 auto-HCT with chemotherapy and prospective cohort studies. Meta-analyses of these studies and trials 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 NRM experienced by patients in the transplantation group.

SUMMARY OF EVIDENCE

For individuals who have cytogenetic or molecular intermediate- or poor-risk acute myeloid leukemia (AML) in first complete remission (CR1) who receive allogeneic (allo) hematopoietic cell transplant (HCT) with myeloablative conditioning (MAC), the evidence includes systematic reviews, randomized controlled trials (RCTs) and matched cohort studies. Relevant outcomes are overall survival and disease-specific survival. The majority of 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. One RCT found no difference in OS between allo-HCT and high-dose cytarabine, although the study had many limitations. 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 myeloablative conditioning, 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 auto-HCT with myeloablative conditioning, 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 allogeneic HCT improves OS rates in patients with relapsed AML better than conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission and for medical reasons cannot tolerate a myeloablative conditioning regimen who receive allo-HCT with reduced-intensity conditioning (RIC), the evidence includes two RCTs, two meta-analyses, and other comparative and non-comparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. The RCTs compared RIC with myeloablative conditioning (MAC) and reported similar rates in non-relapse mortality, relapse, and overall survival, though 1 of the trials was stopped prematurely due to 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 BPDCN allogeneic hematopoietic cell transplantation (HCT) should be considered when patients have achieved a complete remission, the evidence includes a retrospective study where 15 patients diagnosed with BPDCN who underwent an allo-HCT with myeloablative conditioning (MAC). Nine patients were in complete remission (CR)1 and six patients were in CR2 status prior to HCT. All patients received the MAC regimen and an unmanipulated graft. All patients successfully engraftment and achieved full donor chimerism. The primary endpoint, overall leukemia-free survival (LFS) rate and overall survival rate was 73.3 ± 10.5%. Allo-HCT with MAC is a valid option for BPDCN patients in complete remission. Two articles critically reviewing treatment modalities for BPDCN states that HCT should be considered when patients have achieved a complete remission and are sufficiently fit. Long-term remissions have been seen with allo-HCT done during the first remission. 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 allogeneic 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 to chemotherapy in all patients. Relevant outcomes are overall and disease-specific survival. Compared with chemotherapy, patients undergoing auto-HCT experienced reduced relapse and improved disease-free survival (DFS) 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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy published expert panel recommendations on the role of hematopoietic cell transplant (HCT) in newly-diagnosed adult acute myeloid leukemia (AML).(49) Recommendations were generated based on findings from a systematic review and graded based on prespecified criteria. Expert panel recommendations regarding allogeneic HCT (allo-HCT) and autologous HCT and the grades of the recommendations are as follows:

- Patients with unfavorable-risk in first remission (CR1) should undergo allo-HCT. (Grade A)
- Patients with intermediate-risk in CR1 should undergo allo-HCT. (Grade B)
- Patients with favorable-risk in CR1 should not undergo allo-HCT. (Grade C)
- The role of secondary mutational abnormalities in selecting a patient for allo-HCT is unclear. (Grade N/A)
- The presence of measurable residual disease at the end of induction therapy should be considered an indication to offer allo-HCT. (Grade C)
- The role of allo-HCT is unclear in patients with induction failure. (Grade N/A [not applicable])
- Patients with secondary acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)
- Patients with therapy-related acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)
- Patients ≥ 60 years in CR1 should undergo allo-HCT. (Grade B).
- Autologous HCT is a good alternative to chemotherapy consolidation in patients who are not eligible for allo-HCT. (Grade B)
- Myeloablative conditioning should be the preferred type of conditioning in patients who are fit for myeloablative conditioning, but reduced-intensity conditioning is an acceptable alternative in unfit patients. (Grade D)

In 2015, the American Society for Transplantation and Cellular Therapy (formerly The American Society for Blood and Marrow Transplantation) published guidelines on indications for autologous HCT and allo-HCT.(50) An updated guideline was published in 2020.(61) Table 2 summarizes recommendations for HCT in acute myeloid leukemia from the most recent guideline iteration.

Table 2. Recommendations for the Use of Hematopoietic Cell Transplantation to Treat Acute Myeloid Leukemia

Indication	Allo-HCT[a]	Autologous HCT[a]
AML, age <18 years		
First CR, low risk	N	N
First CR, intermediate risk	C	N
First CR, high risk	S	N
Second or greater CR	S	N
Not in remission	S	N
AML, age ≥18 years		
First CR, low risk	N	C
First CR, intermediate risk	S	C
First CR, high risk	S	N
Second CR	S	C
Third or greater CR	S	N
Not in remission	S	N

[a] Recommendations were classified as follows: S, standard of care (well-defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies); C, standard of care, clinical evidence available (large clinical trials are not available; however, sufficiently large cohort studies have shown efficacy with acceptable risk of morbidity and mortality); N, not generally recommended allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; CR: complete remission; HCT: hematopoietic cell transplantation

In 2022, the American Society of Transplantation and Cellular Therapy published guidance on the role of HCT in pediatric AML and myelodysplastic syndrome.(59) The guidelines state that HCT is recommended for patients in CR1 with unfavorable mutations/cytomolecular abnormalities but not for patients with favorable-risk lesions. HCT should also be considered for patients with primary induction failure, refractory disease after 2 to 3 cycles of chemotherapy, and relapse.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines (v.3.2024) (2) for acute myeloid leukemia state that allogeneic HCT is recommended for patients aged <60 years after standard-dose cytarabine induction with induction failure or significant residual disease without a hypocellular marrow. It is also recommended after high dose cytarabine inductions with induction failure, or as post-remission therapy in those with intermediate-risk or poor-risk cytogenetics. Allo-HCT is identified as a "reasonable option" for patients aged ≥60 years after standard-dose cytarabine induction with residual disease or induction failure or following complete response (preferably in a clinical trial). In addition, allo-HCT is recommended for relapsed or refractory disease.

According to the guidelines, the role of autologous HCT is diminishing due to improvements in allo-HCT that have expanded the pool of potential donors outside the family setting. Autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial.

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) (Age ≥18 years) (algorithm)
Following complete remission, consider Allogeneic HSCT, Autologous HSCT (BPDCN-2)

General Principles of BPDCN
Studies suggest that being in first remission (CR1) during receipt of allogeneic HCT significantly enhances the median OS. Reduced intensity conditioning may be considered in patients who achieve CR but cannot tolerate myeloablative transplantation. (BPDCN-A)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
N/A

ONGOING AND UNPUBLISHED CLINICAL TRIALS
No clinical trials that would influence this review were found.

Government Regulations
National:

Medicare National Coverage Determinations Manual, "Stem Cell Transplantation (Formerly 110.8.1) (110.23)" Effective date: 3/06/24; Implementation Date: 10/7/24 (Medicare section has been condensed. See Determination for more information)

Indications and Limitations of Coverage
A.. Nationally Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)

a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,

II. Autologous STEM CELL Transplantation (AuSCT)

a) Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §I862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:
   1. Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched;

B. Nationally Non-Covered Indications

I. Autologous STEM CELL Transplantation (AuSCT)

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:
a) Acute leukemia not in remission;
b) Chronic granulocytic leukemia;

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §I862(a)(1)(A) of the Act and is not covered under Medicare.

Local:

There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT - Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas, Autologous
- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Cell Lymphocytic Lymphoma – Autologous and Allogeneic
- BMT – Hematopoietic Cell Transplantation for CNS Tumors, Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias, Allogeneic
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas, Autologous
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Allogeneic
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma, Plasma Cell Leukemia, Plasmacytoma, and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant

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9(4): 519-526. PMID 36757706

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 27, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Topic split out from former combined autologous and allogeneic bone marrow transplant policies. • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section.
3/1/14	12/10/13	1/6/14	• Routine review. Policy statement unchanged.
7/1/15	4/24/15	5/8/15	• Routine maintenance
7/1/16	4/19/16	4/19/16	• Routine maintenance
1/1/17	10/11/16	10/11/16	• Routine maintenance
1/1/18	10/19/17	10/19/17	• Routine maintenance • Hematopoietic Stem Cell Transplant (HSCT) changed to hematopoietic cell transplant (HCT) throughout policy, including title. • References and rationale updated • Updated Medicare NCD
1/1/19	10/16/18	10/16/18	• Routine maintenance • 38220 and 38221 removed r/t nomenclature change (for diagnostic purposes only)
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance
1/1/23	10/18/22		Routine maintenance (ky)
5/1/23	3/29/23		•The diagnosis code for BPDCN C86.4 was added to the list of payable diagnosis on this policy. Added the below the below under the Inclusions section: o Allogeneic hematopoietic cell transplantation (HCT) in patients with blastic plasmacytoid dendritic cell neoplasm following complete remission.

			•Added section on BPDCN pg 16 and 19 under Summary of Evidence. Vendor review: NA Post JUMP: Updated Description/Background section to include BPDCN. Added BPDCN to the title. Title updated from “BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia” to “BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic plasmacytoid dendritic cell neoplasm (BPDCN)”. Updated MPS to include BPDCN. Added the below: under Inclusions section under Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen for patients with one of the following: o Blastic plasmacytoid dendritic cell neoplasm (BPDCN) following first complete remission CR1 Added the below: under Inclusions section under Allogeneic hematopoietic cell transplantation (HCT) using a reduced-intensity conditioning regimen in patients with one of the following: o BPDCN - reduced intensity conditioning may be considered in patients who achieve CR but cannot tolerate myeloablative transplantation Removed the below that was added prior to JUMP under the Inclusions section: o Allogeneic hematopoietic cell transplantation (HCT) in patients with blastic plasmacytoid dendritic cell neoplasm following complete remission. (ky)
1/1/24	10/17/23		Routine maintenance Vendor: N/A (ky)

1/1/25	10/15/24		Minor Edits - added the below paragraph under Policy Guidelines: o Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HSCT. These include patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient whose disease relapses following a conventional myeloablative allogeneic HSCT could undergo a second myeloablative procedure if a suitable donor is available and the patient's medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HSCT if a complete remission could be re-induced with chemotherapy. Routine maintenance Vendor: N/A (ky)

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT – HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA AND BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. For an approved, preauthorized transplant, BCN will cover the necessary hospital, surgical, lab and X-ray services for a non-member donor, including charges for donating the bone marrow, under the BCN member's certificate, unless the non-member donor has coverage for such services. This also includes solid organ donor procurement fees. Donor travel, meals and lodging expenses are *not* covered unless the BCN member has a rider that covers such services. BCN does NOT cover expenses incurred by a BCN member for donating bone marrow, stem cells or a solid organ (e.g., kidney, liver lobe, lung lobe) to a non-BCN member. The donor services would be considered not medically necessary for the BCN member.
BCNA (Medicare Advantage)	Refer to Medicare section. For an approved, preauthorized transplant, BCNA will cover the necessary hospital, surgical, lab and X-ray services for a non-member donor, including charges for donating the bone marrow, under the BCNA member's certificate, unless the non-member donor has coverage for such services. Donor travel, meals and lodging expenses are covered.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.