# MEDICAL POLICY

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA |
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| POLICY NUMBER | MP 9.040 |

| Effective Date: | 8/1/2023 |
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## I. POLICY

Allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen may be considered **medically necessary** to treat:

- Poor- to intermediate-risk Acute Myeloid Leukemia (AML) in first complete remission (CR1) (see Policy Guidelines section for information on risk stratification); or
- AML that is refractory to standard induction chemotherapy, but can be brought into CR with intensified induction chemotherapy; or
- AML that relapses following chemotherapy-induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy; or
- AML in patients who have relapsed following a prior autologous 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 individuals 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).

Autologous HCT may be considered **medically necessary** to treat AML in CR1 or beyond, or relapsed AML, if responsive to intensified induction chemotherapy in patients who are not candidates for allogeneic HCT.

Allogeneic and autologous HCT are **investigational** in individuals not meeting any of the above criteria, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

### Policy Guidelines

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Primary refractory acute myeloid leukemia (AML) is defined as leukemia that does not achieve a complete remission after conventionally dosed (non-marrow ablative) chemotherapy.

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

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

- Treatment-related AML (secondary to prior chemotherapy and/or radiotherapy for another malignancy)
- AML with antecedent hematologic disease (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 Table PG1.

| **Table PG1. Risk Status of AML Based on Genetic FactorsRisk Status** | **Genetic Abnormality** |
|---|---|
| **Favorable** | t(8;21)(q22;q22.1); RUNX1-RUNX1T1<br>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11<br>Biallelic mutated CEBPA<br>Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow |
| **Intermediate** | Mutated NPM1 and FLT3-ITDhigh<br>Wild-type NPM1 without FLT3-ITD or with FLT3-ITDlow (without adverse-risk genetic lesions)<br>t(9;11)(p21.3;q23.3); MLLT3-KMT2A<br>Cytogenetic abnormalities not classified as favorable or adverse |
| **Poor** | t(6;9)(p23;q34.1); DEK-NUP214<br>t(v;11q23.3); KMT2A rearranged<br>t(9;22)(q34.1;q11.2); BCR-ABL1<br>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)<br>-5 or del(5q); -7; -17/abn(17p)<br>Complex karyotype, monosomal karyotype |

| | |
|---|---|
| | Wild-type NPM1 and FLT3-ITDhigh<br>Mutated RUNX1 (if not co-occurring with favorable-risk AML subtypes)<br>Mutated ASXL1 (if not co-occurring with favorable-risk AML subtypes)<br>Mutated TP53 |

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

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

The ideal allogeneic donors are human leukocyte antigen (HLA) –identical siblings, matched at the HLA-A, -B, and -DR loci (6 of 6). Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, for which there usually is sharing of only 3 of the 6 major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

***Cross-reference:***

**MP 9.001** Placental/Umbilical Cord Blood as a Source of Stem Cells.

## II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

## III. DESCRIPTION/BACKGROUND

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### Acute Myeloid Leukemia

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 HCT. Hematopoietic cell transplantation 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.

**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 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. Cord blood is discussed in detail in MP 9.001.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (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.

*Conventional Conditioning for HCT*

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 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 events. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential 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. 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 of cytotoxic druge or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. R educed-intensity conditioning 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 recent advances in the classification of AML, the genomics of AML and prognostic factors, and current and new treatments. 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.

## 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.

## IV. RATIONALE

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### 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 randomized controlled trials (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 CR1 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 CR-1 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 and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning, the evidence includes 2 randomized controlled trials, 3 meta-analyses, and other comparative and noncomparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. The RCTs 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 CR1 or beyond 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.

## V. DEFINITIONS

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**ALLOGENIC** refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient. These cells are harvested from a donor, after verifying the donor and the recipient are well matched with respect to human leukocyte antigens (HLA).

Allogeneic cells provide two (2) theoretical advantages: the lack of tumor contamination associated with autologous stem cells, and the possibility of a beneficial graft-versus-tumor effect. Their disadvantage is the risk of graft-versus host disease (GVHD), which increases with great HLA disparity and recipient age.

**AUTOLOGOUS** refers to originating within an individual, i.e., self-donation. These stem cells are harvested from patients prior to myeloablative therapy.

**REDUCED-INTENSITY ALLOGENIC STEM CELL TRANSPLANTATION** uses lower doses of chemotherapy than standard allogenic transplant, it does not completely inactivate the patient's immune system or treat the ALL as aggressively. Older, sicker patients may be helped with this type of treatment.

**RELAPSED** refers to patients who have achieved remission but later have decreased numbers of normal blood cells and a return of leukemia in their bone marrow

**REFRACTORY** refers to patients who have residual leukemia cells in their bone marrow even after they receive intensive treatment

## VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

## VII. DISCLAIMER

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*Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

## VIII. CODING INFORMATION

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

**Covered when medically necessary:**

| Procedure Codes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| S2140 | S2142 | S2150 | 38204 | 38205 | 38206 | 38207 | 38208 | 38209 |
| 38210 | 38211 | 38212 | 38213 | 38214 | 38215 | 38230 | 38232 | 38240 |
| 38241 | 38242 | | | | | | | |

| ICD-10-CM Diagnosis Code | Description |
|---|---|
| C92.00 | Acute myeloblastic leukemia, not having achieved remission |
| C92.01 | Acute myeloblastic leukemia, in remission |
| C92.02 | Acute myeloblastic leukemia, in relapse |
| C92.40 | Acute promyelocytic leukemia, not having achieved remission |
| C92.41 | Acute promyelocytic leukemia, in remission |
| C92.42 | Acute promyelocytic leukemia, in relapse |
| C92.50 | Acute myelomonocytic leukemia, not having achieved remission |
| C92.51 | Acute myelomonocytic leukemia, in remission |
| C92.52 | Acute myelomonocytic leukemia, in relapse |
| C92.60 | Acute myeloid leukemia with 11q23-abnormality not having achieved remission |
| C92.61 | Acute myeloid leukemia with 11q23-abnormality in remission |
| C92.62 | Acute myeloid leukemia with 11q23-abnormality in relapse |
| C92.A0 | Acute myeloid leukemia with multilineage dysplasia, not having achieved remission |
| C92.A1 | Acute myeloid leukemia with multilineage dysplasia, in remission |
| C92.A2 | Acute myeloid leukemia with multilineage dysplasia, in relapse |

## IX. REFERENCES

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## X. POLICY HISTORY

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|---|---|
| **MP 9.040** | **CAC 5/20/14 Minor review**. Information related to HSCT for Acute Myeloid Leukemia extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation and this new separate policy created. No change to policy statements. Policy guidelines added. References updated. |
| | **CAC 6/2/15 Consensus review**. No change to policy statements. References and rationale updated. No coding changes. |

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| | **CAC 5/31/16 Minor revision**. Clarification added to the policy statements to mirror BCBSA. Description/Background, Rationale, and References updated. Coding reviewed/updated. |
| | **1/1/17 Admin update.** Product variation section reformatted. |
| | **CAC 7/25/17. Consensus review**. No change to policy statements. NCD updated. References and rationale reviewed. Coding reviewed. |
| | **1/1/18 Admin Update**. Medicare variations removed from Commercial Policies. |
| | **4/27/18 Consensus review**. No change to policy statements. References and background updated. Rationale condensed. "Stem" removed from title and policy. HSCT changed to HCT in Policy and Policy Guidelines |
| | **4/15/19 Admin update**. Coding update. S2140 added to policy. |
| | **5/21/19 Minor review**. Added clarification to the policy statement to match BCBSA. Added code 38207 to match BCBSA policy. Updated references**.** |
| | **05/22/20 Consensus review**. NCCN reference updated. No changes to policy statements. |
| | **3/17/21 Consensus review.** Policy statement unchanged. Revised table PG1 and description background section. References updated. |
| | **2/8/22 Consensus review.** NCCN statement added, no changes to current criteria. No references added. |
| | **2/21/23 Consensus review.** No changes to policy stance. New definitions and updated references. |

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