Molina Clinical Policy
Haploidentical Allogeneic Hematopoietic Cell Transplantation in Blood Cancers: Policy No. 362

Last Approval: 4/13/2023
Next Review Due By: April 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Acute Myeloid Leukemia (AML) is the most common form of acute leukemia in adults – AML is also known as acute myelogenous leukemia and acute nonlymphocytic leukemia. Subtypes of AML are determined by the maturity of the cancer cells. The disease is categorized as untreated, in remission, refractory, or recurrent; there is no staging system for AML. Acute promyelocytic leukemia (APL) is a subtype of AML that occurs when genes on chromosome 15 change places with some genes on chromosome 17 resulting in an abnormal gene called PML-RARA. The PML-RARA gene directs a message to stop promyelocytes (a type of white blood cell) from maturing. This type of AML is most common in middle-aged adults. ([1-2] NCI, 2022). The median age at diagnosis of AML is 68 years. Overall survival (OS) rate at five years is 30% however this can vary by age group; younger patients have an OS of nearly 50% while it is less than 10% in patients over age 60. The OS may be improving due to the FDA approval of 11 drugs or drug combinations. Research has also advanced with respect to the evolution, progression, and resistance mechanisms of AML that will aid in the diagnosis, classification, and monitoring of patients. (Shimony et al., 2023).

Treatment for AML may include chemotherapy, chemotherapy with stem cell transplant, radiation therapy, targeted therapy, or other drug therapy. Drug therapy used for the treatment of APL may include arsenic trioxide and all-trans retinoic acid (ATRA) – anticancer drugs target leukemia cells by destroying them, stopping them from dividing, or by aiding leukemia cells to mature into white blood cells. New treatments are actively being tested in clinical trials. When not treated, AML will get worse rapidly. ([1-2] NCI, 2022). HCT is preferred in individuals less than 60 years of age with intermediate or unfavorable prognoses. When a donor is available, allogeneic HCT is preferred over autologous HCT. Recipients should be monitored for signs or symptoms of acute or chronic GVHD. (Vakiti & Mewawalla, 2023).

Allogeneic hematopoietic cell transplantation (HCT) may cure a broad variety of malignant and non-malignant hematologic disorders. The hematopoietic stem cells required are typically obtained from a related or unrelated donor's bone marrow or peripheral blood. For best outcomes, the stem cell donor is a human leukocyte antigen (HLA)-matched sibling. Potential donors include biological parents; biological children; full or half siblings; and even extended family donors such as aunts, uncles, nieces, nephews, cousins, or grandchildren. There is a 25 percent chance that a sibling will match the patient in developing nations. When there is not an HLA-matched sibling, alternative sources of donor grafts may be used including, but not limited to suitably HLA-matched adult unrelated donors, umbilical cord blood stem cells, and partially HLA-mismatched, or HLA-haploidentical, related donors. Challenges of an HLA-haploidentical HCT include the intense bi-directional alloreactivity leading to high incidences of graft rejection and graft-versus-host disease (GVHD). Due to advances in graft engineering and pharmacologic prophylaxis of GVHD, risks are reduced of graft failure and GVHD. (Fuchs & Luznik, 2021).

COVERAGE POLICY

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be reviewed by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, State regulations, and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.
Haploidentical allogeneic HCT **may be considered a medically necessary** option when there are no matched sibling or unrelated donors for the following blood cancers (AMR, 2020):*

1. Acute Myelogenous Leukemia (AML); **OR**
2. Aplastic Anemia and other Bone Marrow Failure Disorders; **OR**
3. Hodgkin's Lymphoma

HLA-haploidentical donor selection criteria incudes **ALL** of the following:

1. Donor must be medically, socially, and psychologically fit to donate; **AND**

2. Donor age <40 years preferred over donor age ≥40 years; **AND**

3. No major ABO incompatibility between donor and recipient; major ABO incompatibilities include:
   a. Recipient blood type O: Donor type A, B, or AB; **OR**
   b. Recipient blood type A: Donor blood type B or AB; **OR**
   c. Recipient blood type B: Donor blood type A or AB; **OR**
   d. Recipient blood type AB: No major ABO incompatibilities

AND

4. Matched CMV IgG serologic status between donor and recipient include:
   a. For a recipient who is CMV IgG negative, use a CMV IgG negative donor; **OR**
   b. For a recipient who is CMV IgG positive, use a CMV IgG positive donor

AND

5. Use an ABO compatible donor over a minor ABO incompatible donor (ABO compatible transplants are O→O, A→A, B→B, or AB→AB).

*Note: Please see the specific MCP for clinical criteria for each of the above diagnoses

For Members with Significant or Daily Cannabis Use

1. Documentation of compliance with a physician prescribed and managed program of abstinence, and a reasonable expectation that the Member will be abstinent from cannabis use during the transplant and immediate post-transplant time-period. Daily cannabis use is an absolute contraindication for both transplant and pre-transplant evaluation unless there is a state mandate applicable for medical cannabis use and transplants, and there is documentation of Member compliance with a physician prescribed plan of care for prescribed cannabis use.
2. If the Member's cannabis use follows a formal, State-based program for managed medical cannabis, the request should include:
   - Documentation of the Plan of Care for medical cannabis (including the medical decision making that supports the use of medical cannabis); **AND**

- Transplant Provider agreement with the Plan of Care (including agreement to be accountable for managing the Member's use of medical cannabis).

Limitations and Exclusions

Absolute contraindications to the use of a specific HLA-haploidentical donor include:

1. Donor is medically or psychologically unfit; **AND**
2. Recipient has anti-donor HLA antibodies of sufficient strength to result in a positive crossmatch result by flow cytometry or by complement-dependent cytotoxicity assay; **AND**

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

At the current time, there are no published randomized controlled trials of haploidentical HCT that compare either umbilical cord blood HCT or mismatched unrelated donor HCT. For patients with acute leukemia in complete remission or with lymphoma, the United States Blood and Marrow Transplant Clinical Trials Network conducted a phase III, randomized trial of reduced intensity conditioning and transplantation of either double unrelated donor umbilical cord blood or HLA-haploidentical bone marrow (BMT CTN 1101; NCT01597778). The results of this trial have not yet been published. Data regarding outcomes are mostly from retrospective analyses and large multi-institutional studies comparing post-transplant GVHD, transplant related mortality, disease-free survival, or relapse.

Ganser (2023) reported on a large prospective multi-institutional observational study that examined the influence of age, comorbidities, genetic risk, and remission status on patient outcome. Additional factors examined include frailty, impaired quality of life, depression, and diminished functional status. A total of 692 patients were included; 43% were age 65 and older. Forty-six percent of the cohort underwent HCT with a 4-year survival rate of 54%. After adjusting for AML- and patient-specific variables, no benefit of HCT was identified in all older and medically infirm patients compared to patients with European LeukemiaNet adverse risk and those who were never in first complete remission (CR1). Patients aged 60 and older, HCT in CR1 is recommended at diagnosis for patients with intermediate- and adverse-risk disease who are able and willing to undergo remission-inducing therapy. The recommendation is based on large prospective, nonrandomized US and British studies in which patients received conventional induction chemotherapy. Further support is found in the only prospective randomized phase 3 trial initiated by the European Blood and Marrow Transplantation Group (EudraCT-Number 2007-003514-34). This included patients over age 60 years with AML in CR1 after conventional induction and early consolidation chemotherapy who received reduced-intensity conditioning with 2 Gy total body irradiation and fludarabine (RIC) HCT or an additional consolidation chemotherapy (with a superior leukemia-free survival in the HCT arm). Additional research is needed on approaches for older adults and those who are medically infirm with AML who are considering HCT.

For additional peer-reviewed studies used in the development and update of this policy, please see the *Reference* section.

National and Specialty Organizations

The **National Comprehensive Cancer Network (NCCN)** published *Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia.* The guidelines note that haploidentical transplantation may be considered a treatment option if no appropriated matched sibling donor is found and the patient is a candidate for HCT. (Category 2A recommendation). The 2023 version did not include any updates to HCT criteria ([1] NCCN, 2023; Shimony et al., 2023).

The **NCCN** also published *Clinical Practice Guidelines in Oncology: Hematopoietic Cell Transplantation* focus on the management of adult patients with malignant disease. The guidelines provide guidance on HCT, including pretransplant recipient evaluation, hematopoietic cell mobilization, and treatment of GVHD to enable the patient and

provider to assess management options pertinent to each individual patient's condition. The 2023 update includes a new section on the Principles of Conditioning for HCT. ([2] NCCN, 2023; Saad et al., 2023).

The **American Society for Transplantation and Cellular Therapy (ASTCT)** recommends preferential use of myeloablative conditioning in eligible patients. A haploidentical related donor marrow graft is preferred over a cord blood unit in the absence of a fully HLA-matched donor. (Dholaria et al., 2021).

The **American Society of Hematology (ASH)** published guidelines on the treatment of newly diagnosed AML in older adults. The ASH recommends that older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allogeneic HSCT (HSCT; allo-HSCT), post-remission therapy is preferred over no additional therapy. Some patients may receive 2 cycles of intensive antileukemic therapy in some settings even if they achieve remission after the first cycle. The ASH panel considered the second cycle of intensive therapy to be post-remission therapy in this setting. (Sekeres et al., 2020).

CODING & BILLING INFORMATION

CPT Codes

CPT	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

4/13/2023	Policy reviewed, no changes to criteria. Replaced “marijuana” with “cannabis”. Updated Overview and Summary of Medical Evidence sections.
4/13/2022	Policy reviewed; included marijuana use under absolute contraindications; updated Summary of Medical Evidence and Reference sections.
4/5/2021	Policy reviewed, no changes to criteria, updated references.
4/23/2020	New policy.

REFERENCES

Government Agencies

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database. Accessed March 13, 2023. https://www.cms.gov/medicare-coverage-database/search.aspx.
2. ClinicalTrials.gov. Double cord versus haploidentical (BMT CTN 1101). Published May 14, 2012. Updated December 1, 2021. Accessed March 13, 2023. https://clinicaltrials.gov/ct2/show/NCT01597778.

Peer Reviewed Publication

1. Ganser A. Role of allotransplantation in older patients with AML. Blood. 2023 Jan 19;141(3):217-218. doi: 10.1182/blood.2022018786. PMID: 36656613.

National and Specialty Organizations

1. Dholaria B, Savani BN, Hamilton BK, Oran B, Liu HD, Tallman MS, et al. Hematopoietic cell transplantation in the treatment of newly diagnosed adult acute myeloid leukemia: An evidence-based review from the American Society of Transplantation and Cellular Therapy. Transplant Cell Ther. 2021 Jan;27(1):6-20. doi: 10.1016/j.bbmt.2020.09.020. PMID: 32966881.
2. Eastern Cooperative Oncology Group (ECOG). Performance status. Accessed March 28, 2023. https://ecog-acrin.org/resources/ecog-performance-status.
3. [1] National Cancer Institute (NCI). Acute myeloid leukemia (PDQ). Updated August 19, 2022. Accessed March 13, 2023. http://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq.

4. [2] National Cancer Institute (NCI). Childhood acute myeloid leukemia / other myeloid malignancies treatment (PDQ). Updated March 4, 2022. Accessed March 13, 2023. https://www.cancer.gov/types/leukemia/patient/child-aml-treatment-pdq.
5. [1] National Cancer Institute (NCI). Childhood Hodgkin's lymphoma treatment (PDQ). Updated March 24, 2023. Accessed March 13, 2023. https://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq.
6. [2] National Cancer Institute (NCI). Hodgkin's lymphoma treatment (PDQ). Updated March 23, 2023. Accessed March 13, 2023. https://www.cancer.gov/types/lymphoma/hp/adult-hodgkin-treatment-pdq.
7. [1] National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Acute myeloid leukemia (ver. 2.2023). Updated March 13, 2023. Accessed March 28, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
8. [2] National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Hematopoietic cell transplantation (HCT) (ver. 3.2022). Updated January 24, 2023. Accessed March 28, 2023. https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf.
9. [3] National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Hodgkin lymphoma (ver. 2.2023). Updated November 8, 2022. Accessed March 13, 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1439.
10. [1] National Marrow Donor Program (NMDP). Patient eligibility for HCT. Accessed March 28, 2023. https://bethematchclinical.org/transplant-indications-and-outcomes/eligibility/.
11. [2] National Marrow Donor Program (NMDP). Transplant consultation timing guidelines. Accessed March 28, 2023. https://bethematchclinical.org/transplant-indications-and-outcomes/referral-timing-guidelines/.
12. [3] National Marrow Donor Program (NMDP). Measuring engraftment. Accessed March 28, 2023. http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx.
13. [4] National Marrow Donor Program (NMDP). HLA matching. Accessed March 28, 2023. http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx.
14. [5] National Marrow Donor Program (NMDP). Disease-specific indications and outcomes. Accessed March 28, 2023. https://bethematchclinical.org/transplant-indications-and-outcomes/.
15. Sekeres MA, Guyatt G, Abel G, Alibhai S, Altman JK, Buckstein R, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020 Aug 11;4(15):3528-3549. doi: 10.1182/bloodadvances.2020001920. PMID: 32761235. PMCID: PMC7422124.
16. Shimony S, Stahl M, Stone RM. Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 Mar;98(3):502-526. doi: 10.1002/ajh.26822. PMID: 36594187.

Other Authoritative Publications

1. AMR Peer Review. Policy reviewed on February 25, 2020 by an Advanced Medical Reviews (AMR) practicing, board-certified physician(s) in the areas of Oncology and Hematology.
2. Fuchs EJ, Luznik L. HLA-haploidentical hematopoietic cell transplantation. Updated July 16, 2021. Accessed March 13, 2023. http://www.uptodate.com.

Other Authoritative Publications (used in the development of this policy)

1. Ahmed S, Kanakry JA, et al. Lower graft-versus-host disease and relapse risk in post-transplant cyclophosphamide-based haploidentical versus matched sibling donor reduced-intensity conditioning transplant for Hodgkin lymphoma. Biol Blood Marrow Transplant. 2019 Sep;25(9):1859-1868. doi: 10.1016/j.bbmt.2019.05.025.
2. Bazarbachi A, Labopin M, Angelucci E, Gülbas Z, Ozdogu H, Arat M, et al. Haploidentical transplant with post-transplant cyclophosphamide for T-cell acute lymphoblastic leukemia: A report from the European Society for Blood and Marrow Transplantation (EBMT) Acute Leukemia Working Party. Biol Blood Marrow Transplant. 2020 May;26(5):936-942. doi: 10.1016/j.bbmt.2020.01.003.
3. Bazarbachi A, Boumendil A, Finel H, Castagna L, Dominietto A, Blaise D, et al. Influence of donor type, stem cell source and conditioning on outcomes after haploidentical transplant for lymphoma - a LWP-EBMT study. Br J Haematol. 2020 Mar;188(5):745-756. doi: 10.1111/bjh.16182.
4. Brissot E, Labopin L, Ehninger G, Stelljes M, Brecht A, Ganser A, et al. Haploidentical versus unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: a report on 1578 patients from the Acute Leukemia Working Party of the EBMT. Haematologica. 2019 Mar;104(3):524-532. doi: 10.3324/haematol.2017.187450.
5. Chen D, Zhou D, Guo D, Xu P, Chen B. Comparison of outcomes in hematological malignancies treated with haploidentical or HLA-identical sibling hematopoietic stem cell transplantation following myeloablative conditioning: A meta-analysis. PLoS One. 2018 Jan 30;13(1):e0191955.
6. Dezern A, Brodsky R. Haploidentical donor bone marrow transplantation for severe aplastic anemia. Hematol Oncol Clin North Am. 2018 Aug;32(4):629-642. doi: 10.1016/j.hoc.2018.04.001.
7. Gauthier J, Poiré X, Gac AC, Leclerc M, Guillaume T, Chalandon Y, et al. Better outcome with haploidentical over HLA-matched related donors in patients with Hodgkin's lymphoma undergoing allogeneic haematopoietic cell transplantation – a study by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy. Bone Marrow Transplant. 2018 Apr;53(4):400-409. doi: 10.1038/s41409-017-0018-z.
8. Hsu J, Artz A, Mayer SA, Guarner D, Bishop MR, Reich-Slotky R, et al. Combined haploidentical and umbilical cord blood allogeneic stem cell transplantation for high-risk lymphoma and chronic lymphoblastic leukemia. Biol Blood Marrow Transplant. 2018 Feb;24(2):359-365. doi: 10.1016/j.bbmt.2017.10.040.
9. Ma YR, Wang WJ, Cheng YF, Zhang YY, Mo XD, Han TT, et al. Impact of ABO incompatibility on outcomes after haploidentical hematopoietic stem cell transplantation for severe aplastic anemia. Bone Marrow Transplant. 2020 Jan 13. doi: 10.1038/s41409-020-0779-7.
10. Marani C, Raiola AM, et al. Haploidentical transplants with post-transplant cyclophosphamide for relapsed or refractory hodgkin lymphoma: The role of comorbidity index and pretransplant positron emission tomography. Biol Blood Marrow Transplant. 2018 Dec;24(12):2501-2508. doi: 10.1016/j.bbmt.2018.07.025.
Yang B, Yu R, Cai L, Guo B, Chen H, Zhang H, et al. Haploidentical versus matched donor stem cell transplantation for patients with hematological malignancies: A systemic review and meta-analysis. Bone Marrow Transplant. 2019 Jan;54(1):99-122. doi: 10.1038/s41409-018-0239-9.
11. Saad A, Loren A, Bolaños-Meade J, Chen G, Couriel D, Di Stasi A, et al. NCCN guidelines® insights: Hematopoietic cell transplantation, version 3.2022. J Natl Compr Canc Netw. 2023 Feb;21(2):108-115. doi: 10.6004/jnccn.2023.0007. PMID: 36791762.
12. Vakiti A, Mewawalla P. Acute myeloid leukemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. 2022 Aug 15. PMID: 29939652. Bookshelf ID: NBK507875.