



Louisiana

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Policy # 00049

Original Effective Date: 01/28/2002

Current Effective Date: 05/10/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia is addressed separately in medical policy 00459.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Allogeneic Hematopoietic Cell Transplant

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplant (allo-HCT) using a reduced-intensity conditioning (RIC) regimen as a treatment of acute myeloid leukemia (AML) in patients who are in complete marrow and extramedullary remission (CR1 or beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning (MAC) regimen to be **eligible for coverage**** (see Policy Guidelines section).

Autologous Hematopoietic Cell Transplant

Based on review of available data, the Company may consider autologous hematopoietic cell transplant (HCT) to treat acute myeloid leukemia (AML) in first complete remission (CR1) or beyond, or relapsed acute myeloid leukemia (AML) if responsive to intensified induction chemotherapy in patients who are not candidates for allogeneic HCT to be **eligible for coverage.****

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When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Allogeneic Hematopoietic Cell Transplant

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplant (allo-HCT) using a myeloablative conditioning (MAC) regimen to treat acute myeloid leukemia (AML) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility will be considered for allogeneic hematopoietic cell transplant (allo-HCT) using a myeloablative conditioning (MAC) regimen to treat acute myeloid leukemia (AML) when ANY of the following criteria are met:

- Poor-to intermediate-risk acute myeloid leukemia (AML) in first complete remission (CR1) (see Policy Guidelines section for information on risk stratification); OR
- Acute myeloid leukemia (AML) that is refractory to standard induction chemotherapy but can be brought into CR with intensified induction chemotherapy; OR
- Acute myeloid leukemia (AML) that relapses following chemotherapy-induced complete remission 1 (CR1) but can be brought into CR2 or beyond with intensified induction chemotherapy; OR
- Acute myeloid leukemia (AML) in patients who have relapsed following a prior autologous hematopoietic cell transplant (HCT), but can be brought into complete remission (CR) with intensified induction chemotherapy and are medically able to tolerate the procedure.

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of allogeneic and autologous hematopoietic cell transplant (HCT) for acute myeloid leukemia (AML) to be **investigational*** for all other indications.

Based on review of available data, the Company considers the use of allogeneic hematopoietic cell transplant (allo-HCT) when patient selection criteria are not met to be **investigational.***

Policy Guidelines

Primary refractory acute myeloid leukemia (AML) is defined as leukemia that does not achieve a complete remission after conventionally dosed (nonmarrow 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 (eg, myelodysplasia)
- Presence of circulating blasts at the time of diagnosis
- Difficulty in obtaining first complete remission with standard chemotherapy
- Leukemias with monocytoid differentiation (French-American-British classification M4 or M5).

The newer, currently preferred, World Health Organization classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers. It attempts to construct a classification that is universally applicable and prognostically valid. The World Health

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Organization system was adapted by National Comprehensive Cancer Network to estimate individual patient prognosis to guide management, as shown in Table PG1.

Table PG1. Risk Status of AML Based on Cytogenetic and Molecular Factors

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i> inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i> Biallelic mutated <i>CEBPA</i> Mutated <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> ^{low}
Intermediate	Mutated <i>NPM1</i> and <i>FLT3-ITD</i> ^{high} Wild-type <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i> ^{low} (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); <i>MLL3-KMT2A</i> Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); <i>DEK-NUP214</i> t(v;11q23.3); <i>KMT2A</i> rearranged t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i> inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM(EV11)</i> -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Wild-type <i>NPM1</i> and <i>FLT3-ITD</i> ^{high} Mutated <i>RUNX1</i> (if not co-occurring with favorable-risk AML subtypes) Mutated <i>ASXL1</i> (if not co-occurring with favorable-risk AML subtypes) Mutated <i>TP53</i>

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-identical siblings, matched at the human leukocyte antigen-A, -B, and -DR loci (6 of 6). Related donors mismatched at 1 locus are also

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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.

Background/Overview

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 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 hematopoietic cell transplantation (HCT) or high-dose or reduced-intensity chemotherapy with allogeneic HCT (allo-HCT). The 2 treatments—autologous HCT and allo-HCT—represent 2 different strategies. The first, autologous HCT, is a “rescue,” but not a therapeutic procedure; the second, allo-HCT, is a “rescue” plus a therapeutic procedure.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

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

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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 the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing 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 cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, 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 the 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 also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

RIC refers to the pretransplant use of lower doses of cytotoxic drugs 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

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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* summarized recent advances in the classification of acute myeloid leukemia, the genomics of acute myeloid leukemia 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale/Source

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.

Summary of Evidence

For individuals who have cytogenetic or molecular intermediate- or poor-risk AML in first complete remission (CR1) who receive allo-HCT with myeloablative conditioning (MAC), the evidence includes RCTs and matched cohort studies. The relevant outcomes are overall survival (OS) and disease-specific survival (DSS). The evidence has revealed that allo-HCT is better at improving OS

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and DSS rates in patients with AML in CR1 than conventional chemotherapy. All trials employed natural randomization based on donor availability and 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. The relevant outcomes are OS and DSS. The evidence would suggest that allo-HCT improves OS and DSS 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 a 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 CR1 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. The relevant outcomes are OS and DSS. The evidence has shown that allo-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 CR1 and for medical reasons cannot tolerate MAC who receive allo-HCT with reduced-intensity conditioning, the evidence includes 2 RCTs, 2 meta-analyses, and other comparative and noncomparative studies. The relevant outcomes are OS, DSS, and treatment-related morbidity. The RCTs compared reduced-intensity conditioning with MAC and reported similar rates in nonrelapse mortality, relapse, and OS though one of the trials was stopped prematurely due to slow accrual of patients. Two retrospective comparative studies found no difference in OS 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.

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For individuals who have AML in CR1 for beyond without a suitable allo-HCT donor who receives 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 OS and DSS. Compared with chemotherapy, patients undergoing autologous HCT experienced reduced relapse and improved disease-free survival rates. The OS 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.

Additional Information

Not applicable.

Supplemental Information

Practice Guidelines and Position Statements

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. 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)
- Patients with secondary acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)

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- 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 Although a formal systematic review was not conducted, evidence was partly used as the basis for the recommendations. The publication reported that none of the authors had any relevant financial conflicts of interest to declare. Table 2 summarizes recommendations for HCT in acute myeloid leukemia.

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

Indication	Allo-HCT ^a	Autologous HCT ^a
<i>AML, age <18 years</i>		
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	C	N
<i>AML, age ≥ 18 years</i>		
First CR, low risk	N	C

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First CR, intermediate risk	S	C
First CR, high risk	S	C
Second CR	S	C
Third or greater CR	C	C
Not in remission	C	N

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 response; HCT: hematopoietic cell transplantation

National Comprehensive Cancer Network

The National Comprehensive Cancer Network clinical guidelines (v.2. 2021)2, for acute myeloid leukemia state that allo-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 induction 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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Medicare National Coverage

The Centers for Medicare & Medicaid Services have the following national coverage determination on the use of cell transplantation for acute myeloid leukemia:

- Allogeneic: "...for the treatment of leukemia, leukemia in remission..."
- Autologous: "Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Unpublished</i>			
NCT00342316	Prospective Controlled Clinical Study of Allogeneic Stem Cell Transplantation with Reduced Conditioning versus Best Standard Care in Acute Myeloid Leukemia in First Complete Remission	340	Jul 2018 (Completed)

NCT: national clinical trial.

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|------------|---|
| 12/06/2001 | Medical Policy Committee review |
| 01/28/2002 | Managed Care Advisory Council approval |
| 06/24/2002 | Format revision. Coverage eligibility unchanged. |
| 03/31/2004 | Medical Director review |
| 04/20/2004 | Medical Policy Committee review. Format revision. |
| 04/26/2004 | Managed Care Advisory Council approval |
| 04/05/2005 | Medical Director review |
| 04/19/2005 | Medical Policy Committee review. Format revision. Coverage eligibility unchanged. Rationale/source revised. |

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05/23/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006	Medical Director Review
08/09/2006	Medical Policy Committee approval, format revisions, addition of FDA/other governmental regulations, references updates. Coverage eligibility unchanged.
07/11/2007	Medical Director review
07/18/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
07/02/2008	Medical Director review
07/16/2008	Medical Policy Committee approval. Coverage eligibility unchanged. Rationale updated. "High-Dose Chemotherapy" removed from policy title.
07/02/2009	Medical Director review
07/22/2009	Medical Policy Committee approval. Extensive revision of coverage section. Updated background/overview, rationale and references.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage statements clarified with new language.

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- 11/03/2016 Medical Policy Committee review
- 11/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 11/02/2017 Medical Policy Committee review
- 11/15/2017 Medical Policy Implementation Committee approval. Removed “stem” from the policy title, coverage statements and text. Added the phrase ‘but can be brought into CR with intensified induction chemotherapy to the last criteria bullet for HCT using a myeloablative conditioning regimen. Added Policy Guidelines section from Blue Cross Blue Shield Association.
- 11/08/2018 Medical Policy Committee review
- 11/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 04/04/2019 Medical Policy Committee review
- 04/24/2019 Medical Policy Implementation Committee approval. Added (CR1 or beyond) as clarification for allogeneic hematopoietic cell transplant patients in complete marrow and extramedullary remission. Policy statement regarding medical necessity for auto-HCT changed to clarify that it applies to patients that are not candidates for allo-HCT. Investigational statement added for patients not meeting allogeneic MN criteria.
- 04/02/2020 Medical Policy Committee review
- 04/08/2020 Medical Policy Implementation Committee approval. Revised investigational statement for the use of allogeneic and autologous hematopoietic cell transplant (HCT) for all other indications by adding “for acute myeloid leukemia” to be specific to this policy content.
- 04/01/2021 Medical Policy Committee review
- 04/14/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020

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by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150, S2152
ICD-10 Diagnosis	C92.00-C92.02, C92.10-C92.12, C92.20, C92.40-C92.42, C92.50-C92.52, C92.60-C92.62, C92.A0-C92.A2

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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