



Louisiana

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 07/12/2021

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: Hematopoietic Cell Transplantation for Acute Myeloid Leukemia is addressed separately in medical policy 00049.

Note: Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia is addressed separately in medical policy 00053.

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.*

Based on review of available data, the Company may consider myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) to be **eligible for coverage**** as a treatment of:

- myelodysplastic syndromes (see Policy Guidelines section) or
- myeloproliferative neoplasms (see Policy Guidelines section).

Based on review of available data, the Company may consider reduced-intensity conditioning allogeneic hematopoietic cell transplantation (allo-HCT) to be **eligible for coverage**** as a risk adaptive treatment of:

- myelodysplastic syndromes or
- myeloproliferative neoplasms

in patients who are at high-risk of intolerance of a myeloablative conditioning regimen (see Policy Guidelines section).

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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 myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) or reduced-intensity conditioning allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that do not meet the criteria in the Policy Guidelines section to be **investigational**.*

Policy Guidelines

Myeloid Neoplasms

Myeloid neoplasms are categorized according to criteria developed by the World Health Organization (WHO). Neoplasms are risk-stratified using the International Prognostic Scoring System (IPSS).

2008 WHO Classification Scheme for Myeloid Neoplasms

1. Acute myeloid leukemia (AML)
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
 - 3.1 Chronic myelogenous leukemia
 - 3.2 Polycythemia vera
 - 3.3 Essential thrombocythemia
 - 3.4 Primary myelofibrosis
 - 3.5 Chronic neutrophilic leukemia

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3.6 Chronic eosinophilic leukemia, not otherwise categorized

3.7 Hypereosinophilic leukemia

3.8 Mast cell disease

3.9 MPNs, unclassifiable

4. MDS/MPN

4.1 Chronic myelomonocytic leukemia

4.2 Juvenile myelomonocytic leukemia

4.3 Atypical chronic myeloid leukemia

4.4 MDS/MPN, unclassifiable

5. Myeloid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*

5.1 Myeloid neoplasms associate with *PDGFRA* rearrangement

5.2 Myeloid neoplasms associate with *PDGFRB* rearrangement

5.3 Myeloid neoplasms associate with *FGFR1* rearrangement (8p11 myeloproliferative syndrome)

2008 WHO Classification of Myelodysplastic Syndromes (MDS)

1. Refractory anemia (RA)

2. RA with ring sideroblasts

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3. Refractory cytopenia with multilineage dysplasia (RCMD)
4. RCMD with ring sideroblasts
5. RA with excess blasts 1 and 2 (RAEB 1 and 2)
6. del 5q syndrome
7. unclassified MDS

Risk Stratification of MDS

Risk stratification for MDS is performed using the IPSS (see Table PG1). This system was developed after pooling data from 7 studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to group patients into either low-risk and high-risk groups (see Table PG2). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group, which includes intermediate-2 and high-risk IPSS groups, treatment goals are slowing disease progression to AML and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β_2 -microglobulin also should be considered after establishing IPSS. If elevated, the prognostic category worsens by 1 category change.

Table PG1. IPSS: Myelodysplastic Syndrome Prognostic Variables

| Variable | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
|------------------|------|--------------|------|-------|-------|
| Marrow blasts, % | <5 | 5-10 | NA | 11-20 | 21-30 |
| Karyotype | Good | Intermediate | Poor | NA | NA |
| Cytopenias | 0/1 | 2/3 | NA | NA | NA |

NA: not applicable.

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Table PG2. IPSS: Myelodysplastic Syndrome Clinical Outcomes

| Risk Group | Total Score | Median Survival, y | Time for 25% of patients to Progress to AML |
|-------------------|--------------------|---------------------------|--|
| Low | 0 | 5.7 | 9.4 years |
| Intermediate-1 | 0.5-1.0 | 3.5 | 3.3 years |
| Intermediate-2 | 1.5-2.0 | 1.2 | 1.12 years |
| High | ≥2.5 | 0.4 | 0.2 years |

AML: acute myelocytic leukemia

An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS. This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has also been an investigation into using the 5-category IPSS to better characterize risk in MDS.

Given the long natural history of MDS, allogeneic hematopoietic cell transplantation (allo-HCT) is typically considered in patients with increasing numbers of blasts, signaling a possible transformation to AML. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for allo-HCT when chromosomal abnormalities are present, or when the disorder is associated with the development of significant cytopenias (eg, neutrophils $<500/\text{mm}^3$, platelets $<20,000/\text{mm}^3$).

Patients with MPN may be considered candidates for allo-HCT when there is a progression to myelofibrosis or toward acute leukemia. In addition, allo-HCT may be considered in patients with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder. Use of allo-HCT should be based on the following criteria: cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some patients for whom a conventional myeloablative allo-HCT could be curative may be candidates for reduced-intensity conditioning allo-HCT. They include patients whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive

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chemotherapy, low Karnofsky Performance Status) preclude the use of a standard myeloablative conditioning regimen. The ideal allogeneic donors are human leukocyte antigen (HLA)–identical siblings, matched at the HLA-A, -B, and -DR loci (6/6). 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, who usually share 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 graft-versus-host disease extensive as that with matched donors.

Evidence and clinical guidelines suggest reduced-intensity conditioning allo-HCT may be considered as a risk-adapted strategy for high-risk patients of MAC-intolerance as follows:

MDS

- Older age
- IPSS intermediate-2 or high risk
- Multiple comorbidities (e.g., HSCT-comorbidity index (HCT-CI) score higher than 2)
- Red blood cell transfusion dependence
- Neutropenia
- Thrombocytopenia
- High-risk cytogenetics
- Increasing blast percentage

MPN

- Cytopenias
- Transfusion dependence
- Increasing blast percentage over 5%
- Age 60 to 65 years.

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Background/Overview

Myelodysplastic Syndromes

MDS can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insults. Chromosomal abnormalities are seen in 40% to 60% of patients, frequently involving deletions of chromosome 5 or 7 or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 60 years, with an age-adjusted incidence of 62% among individuals older than age 70 years. Patients succumb either to disease progression to acute myeloid leukemia (AML) or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

Myelodysplastic Syndrome Classification and Prognosis

The French-American-British system was used to classify MDS into 5 subtypes: (1) refractory anemia; (2) refractory anemia with ringed sideroblasts; (3) refractory anemia with excess blasts; (4) refractory anemia with excess blasts in transformation; and (5) chronic myelomonocytic leukemia. The French-American-British system was supplanted by that of the World Health Organization (WHO), which records the number of lineages in which dysplasia is seen (unilineage vs. multilineage), separates the 5q-syndrome, and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20%.

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS), which groups patients into 1 of 4 prognostic categories based on the number of cytopenias, cytogenetic profile, and the percentage of blasts in the bone marrow. This system underweights the clinical importance of severe, life-threatening neutropenia and thrombocytopenia in therapeutic decisions and does not account for the rate of change in critical parameters (eg, peripheral blood counts, blast percentage). However, the IPSS has been useful in a comparative analysis of clinical trial results and its utility confirmed at many institutions. An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS. This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has been an investigation into using the 5-category IPSS to better characterize risk in MDS. A second prognostic scoring system

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incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO classification-based Prognostic Scoring System uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML. This system is not yet in widespread use in clinical trials.

MDS Treatment

Treatment of nonprogressing MDS has involved best supportive care, including red blood cell and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. An array of therapies are now available to treat MDS, including hematopoietic growth factors (eg, erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (eg, FDA-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (eg, lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (eg, cytarabine), and allogeneic hematopoietic cell transplantation (allo-HCT). Given the spectrum of treatments available, the goal of therapy must be decided upfront whether it is to improve anemia, thrombocytopenia, or neutropenia, to eliminate the need for red blood cell transfusion, to achieve complete remission, or to cure the disease.

Allo-HCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's risk preference, and severity of MDS at presentation. Allo-HCT is discussed in more detail in a subsequent section.

Chronic Myeloproliferative Neoplasms

Chronic MPN are clonal bone marrow stem cell disorders; as a group, approximately 8400 MPN are diagnosed annually in the United States. Like MDS, MPN primarily occurs in older individuals, with approximately 67% reported in patients aged 60 years and older.

MPN are characterized by the slow but progressive expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. MPN share a common stem cell derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of variants that affects protein tyrosine kinases or related molecules. The unifying characteristic common to all MPN is effective clonal myeloproliferation resulting in peripheral

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granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

MPN Classification

The WHO (2008) classification scheme replaced the term chronic *myeloproliferative disorder* with the term *myeloproliferative neoplasm*. MPN are a subdivision of myeloid neoplasms that includes 4 classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, mast cell disease, and MPN unclassifiable.

MPN Treatment

In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera, and intermediate- and high-risk primary myelofibrosis.

The FDA (2011) approved the orally administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis compared with placebo. The Randomized Study of Ruxolitinib Tablets Compared to Best Available Therapy in Subjects With Primary Myelofibrosis, Post-Polycythemia Vera-Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis (COMFORT-II trial [2013]) compared ruxolitinib with best available therapy in patients who had intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS. In a randomized trial comparing ruxolitinib with best available therapy (including antineoplastic agents, most commonly hydroxyurea, glucocorticoids) with no therapy for treatment of myelofibrosis, Harrison et al (2012) reported improvements in spleen size and quality of life, but not OS.

Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often-severe treatment-related adverse events of this procedure. However, the use of reduced-intensity conditioning (RIC) of conditioning regimens for allo-HCT has extended the potential

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benefits of this procedure to selected individuals with these disorders. Allo-HCT is discussed in more detail in the next section.

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 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 (eg, 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.

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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 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.

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

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) refer to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute

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myelocytic leukemia. Allogeneic hematopoietic cell transplantation (HCT) has been proposed as a curative treatment option for patients with these disorders.

For individuals who have MDS or MPN who receive myeloablative conditioning allogeneic HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of overall and progression-free survival rates, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year OS of 40% to 50% are typical. For HCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis has demonstrated improved survival using HCT compared with standard therapy. At present, HCT is the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS or MPN who receive reduced-intensity conditioning allogeneic HCT, the evidence includes RCTs and retrospective observational series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Evidence from RCT trials and retrospective, nonrandomized comparisons have suggested that reduced-intensity conditioning may be used as a risk-adapted strategy in high-risk patients who are older and have more comorbidities without significantly worsening OS. Reduced-intensity conditioning appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than myeloablative HCT. At present, HCT is the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Supplemental Information **Practice Guidelines and Position Statements**

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network clinical guidelines for myelodysplastic syndromes (v.2.2021) make the following general recommendation about allo-HCT:

“For patients who are transplant candidates, an HLA [human leukocyte antigen]-matched sibling, or HLA-matched unrelated donor can be considered. Results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC [reduced-intensity conditioning] for HCT is generally the strategy in older individuals.”

Specific National Comprehensive Cancer Network recommendations for HCT for treatment of myelodysplastic syndromes are outlined in Table 1.

Table 1. Guidelines for Allo-HCT for Myelodysplastic Syndromes

| Prognostic Category | Recommendations for Allo-HCT |
|--|---|
| IPSS low/intermediate-1 OR IPSS-R very low, low, intermediate OR WPSS very low, low, intermediate | <p>Consider allo-HCT for patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy</p> <p>·Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy</p> |

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| | |
|---|--|
| <p>IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high</p> | <p>· Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available</p> |
|---|--|

allo: allogeneic; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; WPSS: WHO Classification-based Prognostic Scoring System.

Table 2 summarizes the National Comprehensive Cancer Network recommendations (v.1.2020) on the use of allo-HCT for the treatment of myeloproliferative neoplasms. The guidelines note that selection of allo-HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.

Table 2. Guidelines for Allo-HCT for Myeloproliferative Neoplasms

| Prognostic Category | Recommendations for Allo-HCT |
|--|--|
| <p>Intermediate risk - 1 myelofibrosis IPSS=1 DIPSS-Plus=1 DIPSS=1 or 2</p> | <p>· Consider observation or ruxolitinib if symptomatic or allo-HCT. · Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics</p> |
| <p>Intermediate risk - 2 myelofibrosis IPSS=2 DIPSS-Plus=2 or 3 DIPSS=3 or 4 High-risk myelofibrosis IPSS≥3 DIPSS-Plus=4 to 6 DIPSS=5 or 6</p> | <p>· Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. · Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics</p> |
| <p>Disease progression to advanced-stage/AML</p> | <p>· Induce remission with hypomethylating agents or intensive induction chemotherapy followed by allo-HCT</p> |

allo: allogeneic; AML: acute myeloid leukemia; DIPSS: Dynamic International Prognostic Scoring System; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System.

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American Society of Transplantation and Cellular Therapy

In 2015, The American Society of Transplantation and Cellular Therapy (formerly The American Society for Blood and Marrow Transplantation) published guidelines on indications for HCT, based on the recommendations of a multiple-stakeholder task force. Table 3 summarizes categorizations for allo-HCT.

Table 3. Recommendations for the Use of HCT to Treat Myelodysplastic Syndromes, Myelofibrosis, and Myeloproliferative Neoplasms

| Indication | Recommendation |
|---|---|
| Myelodysplastic syndromes | |
| Low/intermediate-1 risk | 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”) |
| Intermediate-2/high-risk | Standard of care (“well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies”) |
| Myelofibrosis and myeloproliferative neoplasms | |
| Primary, low-risk | Standard of care (“well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies”) |
| Primary, intermediate/high-risk | Standard of care (“well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies”) |
| Secondary | Standard of care (“well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies”) |
| Hypereosinophilic syndromes, refractory | Standard of care, rare indication (clinical trials and observational studies are not feasible due to low incidence; small cohorts have shown efficacy with “acceptable risk of morbidity and mortality”) |

HCT: hematopoietic cell transplantation.

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U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is a national coverage determination for stem cell transplantation (110.23; formerly 110.81), portions of which are highlighted below:

Nationally Covered Indications

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

- ...Treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
- ...Treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
- ...Treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study.

- Effective ... January 27, 2016, allogeneic HSCT for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma, and participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source....
- Effective ... January 27, 2016, allogeneic HSCT for myelofibrosis (MF) is covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. All Medicare-approved studies must use appropriate

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statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source....

- f) Effective ... January 27, 2016, allogeneic HSCT for sickle cell disease (SCD) is covered by Medicare only for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical study....”

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|-------------|--|--------------------|-----------------|
| Ongoing | | | |
| NCT00739141 | Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical Cord Blood in Patients with Hematologic Malignancies | 86 | Aug 2021 |
| NCT01760655 | Reduced Intensity Conditioning Before Donor Stem Cell Transplant in Treating Patients with High-Risk Hematologic Malignancies | 72 | Apr 2021 |
| NCT02757989 | Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk | 105 | June 2022 |

NCT: national clinical trial.

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- | | |
|------------|--|
| 01/28/2002 | Managed Care Advisory Council approval |
| 06/24/2002 | Format revision. No substance change to policy. |
| 07/06/2004 | Medical Director review |
| 07/20/2004 | Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Myelodysplastic Diseases and Myeloproliferative Disorders policy developed separately from current HDC with Hematopoietic Stem Cell Support policy. Coverage eligibility unchanged. |
| 07/26/2004 | Managed Care Advisory Council approval |
| 05/03/2005 | Medical Director review |
| 05/17/2005 | Medical Policy Committee review. Coverage eligibility change; “HDC and autologous SCS as initial treatment (i.e., in lieu of an initial course of conventional |

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|------------|--|
| | chemotherapy) of poor-risk germ cell tumors, or as initial treatment of a first relapse (i.e., in lieu of a course of conventional chemotherapy) is investigational”. |
| 05/23/2005 | Managed Care Advisory Council approval |
| 06/07/2006 | Medical Director review |
| 06/21/2006 | Medical Policy Committee approval. Format revisions, FDA/Governmental, Rationale/Source. Coverage eligibility unchanged. |
| 05/02/2007 | Medical Director review |
| 05/23/2007 | Medical Policy Committee approval. No change to coverage eligibility. |
| 10/01/2008 | Medical Director review |
| 10/22/2008 | Medical Policy Committee approval. No change to coverage eligibility. |
| 12/04/2009 | Medical Policy Committee approval |
| 12/16/2009 | Medical Policy Implementation Committee approval. Title changed from “Allogeneic Stem Cell Transplantation of Myelodysplastic and Myeloproliferative Diseases” to “Allogeneic Stem Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms”. Added criteria to the coverage for the treatment of myelodysplastic syndromes. Added criteria to the coverage for the treatment of myeloproliferative neoplasms. Added coverage with criteria for treatment of both myelodysplastic syndromes and myeloproliferative neoplasms. Added reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation to be eligible for coverage. |
| 12/01/2010 | Medical Policy Committee review |
| 12/15/2010 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 12/08/2011 | Medical Policy Committee review |
| 12/21/2011 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 12/06/2012 | Medical Policy Committee review |
| 12/19/2012 | Medical Policy Implementation Committee approval. Added coverage with criteria for allogeneic hematopoietic stem-cell transplantation as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1. |
| 03/04/2013 | Coding updated |
| 12/12/2013 | Medical Policy Committee review |

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| | |
|------------|---|
| 12/18/2013 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/08/2015 | Medical Policy Committee review |
| 01/21/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 04/07/2016 | Medical Policy Committee review |
| 04/20/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 04/06/2017 | Medical Policy Committee review |
| 04/19/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Removed “stem” from stem-cell and added “hematopoietic” into the title. Updated background/rationale and references. |
| 06/07/2018 | Medical Policy Committee review |
| 06/20/2018 | Medical Policy Implementation Committee approval. Clarified the criteria to be diagnoses in each of the Patient Selection Criteria sections. Removed “as a treatment of myelodysplastic syndrome (MDS) and/or myeloproliferative neoplasms (MPNs)” from the investigational statement to clarify that allogeneic HCT is investigational when patient selection criteria are not met. Added FDA/CMS section to our policy. Coverage eligibility unchanged. |
| 06/06/2019 | Medical Policy Committee review |
| 06/19/2019 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/04/2020 | Medical Policy Committee review |
| 06/10/2020 | Medical Policy Implementation Committee approval. Eligible for coverage statement for RIC allo-HCT changed to specify it as a risk-adapted strategy for patients at high-risk of MAC intolerance, which is meant to encompass both older age and medical co-occurring conditions. |
| 06/03/2021 | Medical Policy Committee review |
| 06/09/2021 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

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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 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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CPT is a registered trademark of the American Medical Association.

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, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38242, 38243 |
| HCPCS | S2140, S2142, S2150 |
| ICD-10 Diagnosis | C88.8, C94.40-C94.42, C94.6, D46.0-D46.9, D47.1-D47.9 |

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Louisiana

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 07/12/2021

*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:

- 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

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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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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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