Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 07/08/2024

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 individuals 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).

2022 WHO Classification Scheme for Myeloid Neoplasm and Histiocytic/Dendritic Neoplasms
Clonal hematopoiesis (CH)

- CH of indeterminate potential (CHIP)
- Clonal cytopenia of undetermined significance (CCUS)

Myeloproliferative neoplasms (MPN)

- Chronic myeloid leukemia (CML), BCR-ABL1^{+}
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera
- Primary myelofibrosis (PMF)
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- MPN, not otherwise specified
- Juvenile myelomonocytic leukemia

Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell sarcoma

Childhood MDS

- Childhood MDS with low blasts
  - Hypocellular
  - Not otherwise specified
- Childhood MDS with increased blasts

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- MDS/MPN with neutrophilia
- MDS/MPN with *SF3B1* mutation and thrombocytosis
- MDS/MPN, not otherwise specified

Myelodysplastic neoplasms (MDS)

- MDS with defining genetic abnormalities
  - MDS with low blasts and isolated 5q deletion (MDS-5q)
  - MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*), or MDS with low blasts and ring sideroblasts
  - MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)
- MDS, morphologically defined
  - MDS with low blasts (MDS-LB)
  - MDS, hypoplastic (MDS-h)
  - MDs with increased blasts (MDS-IB)
    - MDS-IB1
    - MDS-IB2
    - MDS with fibrosis (MDS-f)

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Acute myeloid leukemia (AML)

- AML with defining genetic abnormalities
- AML, defined by differentiation

Secondary myeloid neoplasms

- Myeloid neoplasms post cytotoxic therapy
- Myeloid neoplasms associated with germline predisposition

Dendritic cell and histiocytic neoplasms

- Plasmacytoid dendritic cell neoplasms
- Langerhans cell and other dendritic cell neoplasms
- Histiocytic neoplasms

Acute leukemias of ambiguous lineage (ALAL)

- ALAL with defining genetic abnormalities
- ALAL, immunophenotypically defined

Genetic tumor syndromes with predisposition to myeloid neoplasia

Risk Stratification of Myelodysplastic Syndromes

Risk stratification for MDS is performed using the IPSS (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 individuals into either low-risk or high-risk groups (Table PG2). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS individuals 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. International Prognostic Scoring System: Myelodysplastic Syndrome Prognostic Variables

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

NA: not applicable.

Table PG2. International Prognostic Scoring System: 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 to 1.0	3.5	3.3 years
Intermediate-2	1.5 to 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 individuals with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS (see Schanz et al, 2012). 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 individuals 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 CMML.

Individuals 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/mm^3, platelets <20,000/mm^3).

Individuals with myeloproliferative neoplasms 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 individuals 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 individuals for whom a conventional myeloablative allo-HCT could be curative may be candidates for reduced-intensity conditioning (RIC) allo-HCT. These include individuals whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude the use of a standard myeloablative conditioning (MAC) 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 individual , who usually share only 3 of the 6 major histocompatibility antigens. Most individuals will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as GVHD extensive as that with matched donors. Evidence and clinical guidelines suggest RIC allo-HCT may be considered as a risk-adapted strategy for high-risk individuals of MAC-intolerance as follows:

MDS

- Older age
- IPSS intermediate-2 or high risk
- Multiple comorbidities (e.g., hematopoietic cell transplantation -comorbidity index (HCT-CI) score higher than 2)
- Red blood cell transfusion dependence
- Neutropenia

- Thrombocytopenia
- High-risk cytogenetics
- Increasing blast percentage

Myeloproliferative neoplasm

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

Background/Overview

Myelodysplastic Syndromes

Myelodysplastic syndrome (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 previously 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 differentiates between MDS defined by genetic abnormalities or by morphologic features (in the form of dysplastic cell lineages), 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 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.

Myelodysplastic Syndrome Treatment

Treatment of nonprogressing MDS has previously 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, U.S. Food and Drug Administration (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 preference, risk category, and severity of MDS at presentation. Allo-HCT is discussed in more detail in a subsequent section.

Chronic Myeloproliferative Neoplasms
Chronic myeloproliferative neoplasms are clonal bone marrow stem cell disorders; as a group, approximately 8,400 myeloproliferative neoplasms are diagnosed annually in the United States. Like MDS, myeloproliferative neoplasms primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older.

Myeloproliferative neoplasms are characterized by the slow but progressive expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. Myeloproliferative neoplasms 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 myeloproliferative neoplasms is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

Myeloproliferative Neoplasm Classification
Myeloproliferative neoplasms are a subdivision of myeloid neoplasms that includes 4 classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia not otherwise specified, and myeloproliferative neoplasm unclassifiable. In the 2016 classification, mastocytosis is no longer considered a subgroup of the myeloproliferative neoplasms due to its unique clinical and pathologic features.

Myeloproliferative Neoplasm 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. In 2019, the FDA also approved fedratinib (Inrebic®‡) for adults with intermediate-2 or high-risk primary or secondary myelofibrosis based on results from a double-blind, randomized, placebo-controlled trial that found improvement in spleen volume and myelofibrosis-related symptoms.

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) for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders. Allo-HCT is discussed in more detail in the next section.

Hematopoietic Cell Transplantation
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. Human leukocyte antigen 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 (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of 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 GVHD.

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 MAC treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who

undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Description

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms refer to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia. Allogeneic hematopoietic cell transplantation (allo-HCT) has been proposed as a curative treatment option for patients with these disorders

Summary of Evidence

For individuals who have myelodysplastic syndrome (MDS) who receive myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes systemic reviews, randomized controlled trials (RCTs), and numerous 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 hematopoietic cell transplantion (HCT) for MDS have reported a relatively large range of overall and progression free

survival (PFS) 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. Evidence from randomized and nonrandomized comparisons has suggested that RIC may be used as a risk-adapted strategy in high-risk patients who are older and with more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than MAC HCT. At present, HCT is the only potentially curative treatment option for patients with MDS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have myeloproliferative neoplasms who receive MAC or RIC allo-HCT, the evidence includes a systematic review and retrospective observational series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Evidence has suggested that RIC may be used as a risk-adapted strategy in high-risk patients who are older and have more comorbidities without significantly worsening OS. RIC 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 myeloproliferative neoplasms. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

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

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network clinical guidelines for myelodysplastic syndromes (v.1.2024) make the following general recommendation about allogeneic hematopoietic cell transplanatation (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 Allogeneic Hematopoietic Cell Transplantation 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	• Consider allo-HCT for select patients who have clinically relevant thrombocytopenia or neutropenia , with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy • Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL or lower serum erythropoietin level with inadequate response to erythropoetin stimulating agents and/or lenalidomide, with poor probability of or inadequate response/intolerance to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy • Consider allo-HCT for patients who have symptomatic anemia with del(5q), with inadequate response/intolerance to lenalidomide and/or erythropoetin stimulating agents, and no response or

	intolerance to azacitidine/decitabine or immunosuppressive therapy
IPSS intermediate-2, high *OR* IPSS-R intermediate, high, very high *OR* WPSS high, very high	• Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available

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.3.2022) 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 Allogeneic Hematopoietic Cell Transplantation for Myeloproliferative Neoplasms

Prognostic Category	Recommendations for Allo-HCT
Lower-risk myelofibrosis MIPSS-70≤3 MIPSS-70+ Version 2.0 ≤3 DIPSS-Plus ≤1 DIPSS ≤2 MYSEC-PM <14	• In symptomatic patients with disease progression despite treatment with ruxolitinib, peginterferon alfa-2a, and/or hydroxyurea (if cytoreduction would be symptomatically beneficial), consider allo-HCT immediately or bridging therapy 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
Higher-risk myelofibrosis MIPSS-70 ≥4 MIPSS-70+ Version 2.0 ≥4	• Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant

DIPSS-Plus >1 DIPSS >2 MYSEC-PM ≥14	• Evaluation for allo-HCT is recommended for all patients
Disease progression to advanced-stage/AML	• Induce remission with hypomethylating agents ± JAK inhibitors or intensive induction chemotherapy followed by allo-HCT

allo: allogeneic; AML: acute myeloid leukemia; DIPSS: Dynamic International Prognostic Scoring System; HCT: hematopoietic cell transplantation; MIPSS: Mutation-Enhanced International Prognostic Scoring System; MYSEC-PM: Myelofibrosis Secondary to PV [polycythemia vera] and ET [essential thrombocythemia]-Prognostic Model; JAK: Janus kinase.

American Society of Transplantation and Cellular Therapy

In 2020, the American Society of Transplantation and Cellular Therapy (ASTCT) (formerly The American Society for Blood and Marrow Transplantation) published updated guidelines on indications for HCT and immune effector cell therapy based on the recommendations of a multiple-stakeholder task force. Table 3 summarizes categorizations for allo-HCT in adults.

Table 3. Recommendations for the Use of Hematopoietic Cell Transplantation 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 and observational studies 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")

In 2022, the ASTCT published practice recommendations for HCT in the management of myelodysplastic syndromes. A standardized system for grading the levels of evidence was applied (as recommended by the ASTCT Steering Committee for evidence-based reviews). Table 4 summarizes allo-HCT specific recommendations by ASTCT.

Table 4. Recommendations for the Use of Allogeneic Hematopoietic Cell Transplantation to Treat Myelodysplastic Syndromes

Indication/ Consideration	Recommendation	Grade of Recommendation
Should allogeneic HCT routinely be offered early for advanced (int-2/high) de novo MDS?	Yes	A
Should allogeneic HCT routinely be offered early for	No	B

lower risk (low/int-1) de novo MDS?		

HCT: hematopoietic cell transplantation; MDS: myelodysplastic syndrome.

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 versus 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 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….
- 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 ongoing trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02757989	Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk	79	Jun 2024
NCT05367583	Cohort Study Assessing the Treatment Strategy for High-Risk Myelodysplastic Syndromes in Patients Under 70 (COMYRE)	107	Oct 2024

NCT: national clinical trial.

References

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Policy History

Original Effective Date: 01/28/2002
Current Effective Date: 07/08/2024

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 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

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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
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.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2024	Medical Policy Committee review
06/12/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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 2023 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 Delete effective 07/01/2024: 38206, 38232
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related Diagnoses

*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 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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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.