



Louisiana

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

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 reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) as a treatment of myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPNs) in patients who for medical reasons would be unable to tolerate a myeloablative (MA) conditioning regimen to be **eligible for coverage**.

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.*

Based on review of available data, the Company may consider allogeneic HCT as a treatment of MDS to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic HCT as a treatment of MDS will be considered when ANY of the following diagnoses are present:

- Refractory anemia (RA); or
- Refractory anemia with ring sideroblasts (RARS); or
- Refractory cytopenia with multilineage dysplasia (RCMD); or
- RCMD with ring sideroblast; or
- Refractory anemia with excess blasts 1 and 2 (RAEB 1 and 2); or

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- Del 5q syndrome; or
- Unclassified MDS.

Based on review of available data, the Company may consider allogeneic HCT as a treatment of MPNs to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic HCT as a treatment of MPNs will be considered when ANY of the following diagnoses are present:

- Chronic myelogenous leukemia (CML); or
- Polycythemia vera (PCV); or
- Essential thrombocythemia (ET); or
- Primary myelofibrosis (PMF); or
- Chronic neutrophilic leukemia (CNL); or
- Chronic eosinophilic leukemia (CEL), not otherwise categorized; or
- Hypereosinophilic leukemia; or
- Mast cell disease (MCD); or
- MPNs, unclassifiable.

Based on review of available data, the Company may consider allogeneic HCT as a treatment of both MDS and MPNs to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic HCT as a treatment of both MDS and MPNs will be considered when ANY of the following diagnoses are present:

- Chronic myelomonocytic leukemia (CMML); or
- Juvenile myelomonocytic leukemia; or
- Atypical chronic myeloid leukemia; or
- MDS/MPN, unclassifiable.

Based on review of available data, the Company may consider allogeneic HCT as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 to be **eligible for coverage** when the patient selection criteria are met.

Patient Selection Criteria

Allogeneic HCT as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 will be considered when ANY of the following diagnoses are present:

- Myeloid neoplasms associated with PDGFRA rearrangement; OR
- Myeloid neoplasms associated with PDGFRB rearrangement; OR
- Myeloid neoplasms associated with FGFR1 rearrangement (8p11 myeloproliferative syndrome).

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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 allogeneic HCT when patient selection criteria are not met to be **investigational**.*

Background/Overview

MYELODYSPLASTIC SYNDROMES

MDS can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. 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.

MDS Classification and Prognosis

The French-American-British system was used to classify MDS into 5 subtypes: (1) RA; (2) RARS; (3) RAEB; (4) RAEB in transformation; and (5) CMML. 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 (e.g., peripheral blood counts, blast percentage). However, the IPSS has been useful in 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. This system is not yet in widespread use in clinical trials.

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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 (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., Food and Drug Administration [FDA]–approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., 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 MPNs are clonal bone marrow stem cell disorders; as a group, approximately 8400 MPN are diagnosed annually in the United States. Like MDS, MPN primarily occur 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 granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

MPN Classification

In 2008, the WHO 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, PCV, essential thrombocythemia, and PMF. The WHO classification also includes CNL, CEL/hypereosinophilic syndrome, MCD, 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 PCV, and intermediate- and high-risk PMF.

In 2011, the FDA 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,

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spleen size, and symptoms of myelofibrosis compared with placebo. The 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.

MA 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, use of RIC of conditioning regimens 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 stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for HCT

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide [Cy], busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

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Reduced-Intensity Conditioning for Allo-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose MA conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally MA to minimally MA with lymphoablation, and 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, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be non-MA, as opposed to fully MA (conventional) regimens.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. 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.

Centers for Medicare and Medicaid Services (CMS)

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

“B. Nationally Covered Indications

I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

- a) ...Treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
- b) ...Treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
- c) ...Treatment of 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.

- d) 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

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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, GVHD prophylaxis, donor type and cell source....

- e) 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, 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....”

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

MYELODYSPLASTIC SYNDROMES

Myeloablative Conditioning Allogeneic Hematopoietic Cell Transplantation

Despite the successes seen with drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allo-HCT is the only treatment capable of complete and permanent eradication of the MDS clone.

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A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with MAC for MDS. Reviewers selected 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 cases (age range, 32-59 years). Most patients (n=885) received matched-related donor allo-HCT, with other donor types including syngeneic, matched, unrelated donor, mismatched unrelated donor, and umbilical cord blood. Most studies included de novo and secondary MDS, CML, MPN, de novo and secondary AML, and transformed AML. Peripheral blood and bone marrow stem cell grafts were allowed in most studies. The most commonly used conditioning regimens were busulfan plus CY and CY plus total body irradiation, with cyclosporine A (CYA) used for GVHD prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Acute GVHD (grades II-IV) varied from 18% to 100%. Relapse risk ranged from 24% at 1 year to 36% at 5 years. OS rates ranged from 25% at 2 years to 52% at 4 years, with NRM ranging from 19% at day 100 to 61% at 5 years.

A 2009 review from the American Society for Blood and Marrow Transplantation (ASBMT) evaluated the evidence related to HCT in the therapy of MDS, with associated treatment recommendations. Reviewers concluded that outcomes improved with early HCT for patients with an IPSS score of intermediate-2 or high-risk at diagnosis who had a suitable donor and met the transplant center's eligibility criteria, and for selected patients with a low or intermediate-1 risk IPSS score at diagnosis who had a poor prognostic feature not included in the IPSS (i.e., older age, refractory cytopenias). Koenecke et al (2015) evaluated the impact on the revised 5-category IPSS score (IPSS-5) on outcomes after HCT in patients with MDS or secondary AML (evolved from MDS). In a cohort of 903 patients retrospectively identified from the European Society for Blood and Marrow Transplantation database, those with poor and very poor risk had shorter relapse-free survival (RFS) and OS than those with very good, good, or intermediate risk. However, the ways that transplant management strategies should change based on cytogenetic abnormalities are not currently well defined.

Reduced-Intensity Conditioning Allo-HCT for MDS

Evidence from a number of largely heterogeneous, uncontrolled studies of RIC with allo-HCT has shown long-term remission (i.e., >4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with MDS or AML who otherwise would not be candidates for MAC regimens. These prospective and retrospective studies included cohorts of 16 to 215 patients similar to those in the MAC allo-HCT studies. The most common conditioning regimens used were fludarabine-based, with CYA and tacrolimus used for GVHD prophylaxis. The reported incidence of grades II to IV GVHD was 9% to 63%, with relapse risk of 6% to 61%. OS rates ranged between 44% at 1 year and 46% at 5 years (median follow-up range, 14 months to >4 years).

Zeng et al (2014) conducted a systematic review and meta-analysis comparing outcomes for patients who had MDS or AML treated with HCT plus RIC or MAC. Reviewers included 8 studies (2 prospective, 8 retrospective), with a total of 6464 AML or MDS patients. Of these, 171 received RIC and 4893 received MAC. Overall, RIC-treated patients were older and more likely to have multiple comorbidities. In pooled analysis, OS, RFS, and NRM did not differ significantly between patients receiving RIC and MAC. Relapse

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incidence was significantly lower in the MAC arm (odds ratio for RIC vs MAC, 1.41; 95% confidence interval [CI], 1.24 to 1.59; $p < 0.001$).

Aoki et al (2015) compared RIC with MAC in a retrospective cohort of 448 patients (age range, 50-69 years) with advanced MDS (refractory anemia with excess blasts or RA in transformation). Of the total, 197 (44%) and 251 (56%) received MAC or RIC, respectively. The groups differed at baseline: patients who received RIC were significantly more likely to be 60 to 69 years old (vs 50-59 years; 47% for RIC vs 47% for MAC; $p = 0.001$), and less likely to receive an unrelated donor transplant (54% vs 70%; $p = 0.001$). Three-year OS rates did not differ between groups (44.1% for RIC vs 42.7% for MAC; $p = 0.330$). Although patients treated with RIC had a significantly lower 3-year cumulative incidence of NRM (25.6% vs 37.9%; $p = 0.002$), they had significantly higher 3-year incidence of relapse than patients treated with MAC (29.9% vs 22.8%; $p = 0.029$).

In 2012, Kim et al published a phase 3 randomized trial (N=83 patients) comparing toxicity rates for 2 conditioning regimens (reduced CY, fludarabine, and antithymocyte globulin [ATG]; standard CY-ATG). Four patients had MDS, and the remaining patients had severe aplastic anemia. Overall, the incidence of reported toxicities was lower in patients receiving the RIC regimen (23% vs 55%; $p = 0.003$). Subgroup analyses showed no differences in the overall results based on differential diagnosis.

In general, these RIC trials showed a low rate of engraftment failure and low NRM, but a higher relapse rate than with MAC allo-HCT. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with MAC and RIC regimens with allo-HCT. Furthermore, no published randomized trials have compared RIC plus allo-HCT with conventional chemotherapy alone, which has been the standard of care in patients with MDS and AML for whom MAC chemotherapy and allo-HCT are contraindicated.

The ASBMT's 2009 systematic review (previously described) assessed the evidence supporting RIC and MAC regimens and drew the following conclusions: "There are insufficient data to make a recommendation for an optimal conditioning regimen intensity. A range of dose intensities is currently being investigated, and the optimal approach will likely depend on disease and patient characteristics, such as age and comorbidities." Other reviews (2010-2012) have also drawn conclusions similar to those of the ASBMT. Given the absence of curative therapies for these patients, however, RIC allo-HCT may be considered a treatment for patients with MDS who could benefit from allo-HCT but who for medical reasons would not tolerate a MAC regimen.

Outcomes After Allo-HCT in Mixed MDS Populations

A number of studies, primarily retrospective, continue to report outcomes from allo-HCT for MDS in a variety of patient populations and to evaluate the impact of specific patient, conditioning, and donor characteristics on outcomes; representative studies are summarized in Table 1.

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Table 1. Case Series of HCT Treatment for MDS

Study	Patient Population	Type of HCT	Summary of Outcomes
Basquiera et al (2015)	52 pediatric patients with MDS	<ul style="list-style-type: none"> • Allo-HCT (59% with related donors) • Stem cell source: <ul style="list-style-type: none"> ○ Bone marrow, 63% ○ Peripheral blood, 26% ○ Umbilical cord blood, 11% 	<ul style="list-style-type: none"> • 5-y DFS=50% • 5-y OS=55%
Boehm et al (2014)	60 adults with MDS or secondary AML	<ul style="list-style-type: none"> • Allo-HCT • MAC in 36 patients; RIC in 24 patients 	10-y OS=46%
Damaj et al (2014)	128 adults with MDS: 40 received AZA before HCT and 88 received BSC	RIC allo-HCT	<ul style="list-style-type: none"> • 3-y OS=53% in AZA group vs 53% in BSC group (p=0.69) • 3-y RFS=37% in AZA group vs 42% in BSC group (p=0.78) • 3-y NRM=20% in AZA group vs 23% in BSC group (p=0.74)
Di Stasi et al (2014)	227 patients with MDS or AML	<ul style="list-style-type: none"> • Allo-HCT • Donor source: <ul style="list-style-type: none"> ○ Matched-related, 38% ○ Matched-unrelated, 48% ○ Haploidentical, 14% 	3-y PFS for patients in remission: <ul style="list-style-type: none"> • 57% for matched-related • 45% for matched-unrelated • 41% for haploidentical (p=0.417)
Onida et al (2014)	<ul style="list-style-type: none"> • 523 patients with MDS • IPSS cytogenetic risk group: <ul style="list-style-type: none"> ○ Good risk: 53.5% ○ Intermediate risk: 24.5% ○ Poor risk: 22% 	<ul style="list-style-type: none"> • Allo-HCT • RIC in 12% 	5-y OS based on IPSS cytogenetic risk group: <ul style="list-style-type: none"> • Good: 48% • Intermediate: 45% • Poor: 30%
Oran et al (2014)	<ul style="list-style-type: none"> • 256 patients with MDS • Pretreatment: <ul style="list-style-type: none"> ○ No cytoreductive chemo: 30.5% ○ Chemo: 15.6% ○ HMA: 47.7% ○ Chemo + HMA: 6.2% 	<ul style="list-style-type: none"> • Allo-HCT • RIC in 36.7% 	3-y EFS based on cytoreductive therapy: <ul style="list-style-type: none"> • No cytoreductive chemo: 44.2% • Chemo: 30.6% • HMA: 34.2% • Chemo + HMA: 32.8% (p=0.50)
Yoshimi et al (2014)	17 children with secondary MDS or AML after childhood aplastic anemia	• Allo-HCT	5-y OS and EFS=41%
Basquiera et al (2016)	<ul style="list-style-type: none"> • 84 adults with MDS • Cytogenetic risk group: <ul style="list-style-type: none"> ○ Standard: 65.5% ○ Adverse: 12.6% ○ Unknown: 21.9% 	<ul style="list-style-type: none"> • Allo-HCT • RIC in 31.1% 	OS: <ul style="list-style-type: none"> • Median: 23.5 mo (95% CI, 1.7 to 45.3 mo) • 1-y=61% (95% CI, 50% to 70%) • 4-y=38% (95% CI, 27% to 49%) PFS: <ul style="list-style-type: none"> • Median: 19.9 mo (95% CI, 9 to

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Study	Patient Population	Type of HCT	Summary of Outcomes
			31 mo) <ul style="list-style-type: none"> 1-y=57% (95% CI, 46% to 67%) 4-y=37% (95% CI, 26% to 48%)
Symeonidis et al (2015)	<ul style="list-style-type: none"> 513 adults with CMML Pretreatment: <ul style="list-style-type: none"> No prior disease-modifying therapy: 28% Disease-modifying therapy: 72% 	<ul style="list-style-type: none"> Allo-HCT RIC in 41.6% 	<ul style="list-style-type: none"> 1-y NRM=31% 4-y NRM=41% 4-y RFS=27% 4-y OS=33%
Pohlen et al (2016)	<ul style="list-style-type: none"> 187 patients with refractory AML (87%) or high-risk MD (13%) 	<ul style="list-style-type: none"> Allo-HCT RIC in 52% Unrelated donors in 73% Stem cell source: <ul style="list-style-type: none"> Bone marrow, 6% Peripheral blood, 94% 	<ul style="list-style-type: none"> 3-y RFS=32% (95% CI, 25% to 39%) 3-y OS=35% (95%CI, 27% to 42%)
Heidenreich et al (2017)	<ul style="list-style-type: none"> 313 adults with MDS and secondary AML, age ≥ 70 Cytogenetic risk group: <ul style="list-style-type: none"> Good: 51% Intermediate: 22% Poor/very poor: 11% 	<ul style="list-style-type: none"> Allo-HCT RIC or non-MAC in 83% Unrelated donors in 75% Stem cell source: <ul style="list-style-type: none"> Bone marrow, 6% Peripheral blood, 94% 	<ul style="list-style-type: none"> 1-y NRM: 32% 3-y relapse: 28% 3-y OS: 34%

allo; allogeneic; AML: acute myelogenous leukemia; AZA: azacitidine; BSC: best supportive care; chemo: chemotherapy; CI: confidence interval; CMML: chronic myelomonocytic leukemia; DFS: disease-free survival; HMA: hypomethylating agents; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; MAC: myeloablative conditioning; MDS: myelodysplastic syndromes; NRM: nonrelapse mortality; OS: overall survival; RFS: relapse-free survival; RIC: reduced-intensity conditioning.

Section Summary: Myelodysplastic Syndromes

Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of OS and progression-free survival values, 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. Direct comparisons between RIC and MAC prior to HCT with randomly selected populations are not available. Evidence from nonrandomized comparisons has suggested that RIC may be used in patients who are older and with more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of NRM but higher cancer relapse than MAC HCT.

MYELOPROLIFERATIVE NEOPLASMS

Data on therapy for MPN are sparse. As outlined in this evidence review, with the exception of MAC chemotherapy and allo-HCT, no therapy has yet proven to be curative or to prolong survival of patients with MPN.

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The largest study identified evaluating allo-HCT for PMF comes from a 2010 analysis of the outcomes for 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research. Median age was 47 years (range, 18-73 years). Donors were HLA-identical siblings in 162 patients, unrelated individuals in 101 patients, and HLA nonidentical family members in 26 patients. Patients were treated with a variety of conditioning regimens and GVHD prophylaxis regimens. Splenectomy was performed in 65 patients before transplantation. The 100-day treatment-related mortality was 18% for HLA-identical sibling transplants, 35% for unrelated transplants, and 19% for transplants from alternative-related donors. Corresponding 5-year OS rates were 37%, 30%, and 40%, respectively. Disease-free survival (DFS) rates were 33%, 27%, and 22%, respectively. DFS for patients receiving RIC allo-HCT was comparable: 39% for HLA-identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic transplantation for MF resulted in long-term RFS in about one-third of patients.

Gupta et al reported better DFS rates in a 2014 analysis of 233 patients with PMF who underwent RIC HCT from 1997 to 2010. The 5-year OS rate was 47% (95% CI, 40% to 53%). Conditioning regimen was not significantly associated with OS.

In another relatively large study that included patients with PMF who were under 65 years old at diagnosis, Kroger et al (2015) compared outcomes for patients treated with allo-HCT (n=190) or conventional therapies (n=248) at diagnosis. In the HCT group, 91 and 97 subjects received RIC and MAC, respectively. Patients at low risk based on the DIPSS model treated with HCT had a relative risk of death, compared with conventionally treated patients, of 5.6 (95% CI, 1.7 to 19; p=0.005). In contrast, those with intermediate-2 and high-risk disease treated with HCT had a relative risk of death, compared with conventionally treated patients, of 0.55 (95% CI, 0.36 to 0.83; p=0.005) and 0.37 (95% CI, 0.21 to 0.66; p<0.001), respectively. Intermediate-1 patients treated with HCT did not differ significantly in risk of death from those treated with conventional therapies. Although the study design was limited by the potential for bias due to patient selection, these results support using prognosis to guide decisions about HCT for PMF.

The significant toxicity of MAC plus allo-HCT in MPN has led to study of RIC regimens for these diseases. Data from direct, prospective comparison of outcomes of MAC and allo-HCT vs RIC and allogeneic stem cell support in MPN are not available, but single-arm series and nonrandomized comparative studies have reported outcomes after RIC allo-HCT. One 2008 series included 27 patients (mean age, 59 years) with MPN who underwent allo-HCT using an RIC regimen of low-dose (2 gray) total body irradiation alone with or without fludarabine. At a median follow-up of 47 months, 3-year RFS was 37%, 3-year OS was 43%, and 3-year NRM was 32%. In a second series (2009), 103 patients (median age, 55 years; range, 32-68 years) with intermediate-to-high risk (86% of total patients) PMF or post ET and PCV MF were included in a prospective, multicenter, phase 2 trial to determine the efficacy of a busulfan plus fludarabine-based RIC regimen followed by allo-HCT from related (n=33) or unrelated (n=70) donors. Acute GVHD (grade II-IV) occurred in 27% of patients, and chronic GVHD in 43%. The cumulative incidence of NRM at 1 year in all patients was 16% (95% CI, 9% to 23%), but reached 38% (95% CI, 15% to 61%) among those with a mismatched donor vs 12% (95% CI, 5% to 19%) among cases with a matched donor (p=0.003). The

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cumulative relapse rates at 3 and 5 years were 22% (95% CI, 13% to 31%) and 29% (95% CI, 16% to 42%), respectively. After a median follow-up of 33 months (range, 12-76 months), the 5-year estimated DFS and OS rates were 51% (95% CI, 38% to 64%) and 67% (95% CI, 55% to 79%), respectively.

A 2009 retrospective study analyzed the impact of conditioning intensity on outcomes for allo-HCT in patients with MF. This multicenter trial included 46 consecutive patients treated at 3 Canadian and 4 European transplant centers between 1998 and 2005. Twenty-three patients (median age, 47 years; range, 31-60 years) underwent MAC and 23 patients (median age, 54 years; range, 38-74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate or high risk. At a median follow-up of 50 months (range, 20-89 months), there was a trend for a better progression-free survival rate at 3 years in RIC patients than in MAC patients (58% [range, 23%-62%] vs 43% [range, 35%-76%], respectively; $p=0.11$); there was a similar trend in the 3-year OS rate (68% [range, 45%-84%] vs 48% [range, 27%-66%], respectively; $p=0.08$). NRM rates at 3 years trended higher in MAC cases (48%; range, 31%-74%) than in RIC cases (27%; range, 14%-55%; $p=0.08$). The results of this study suggested that both types of conditioning regimens have curative potential in patients with MF. Despite the RIC patients being significantly older, with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allo-HCT in this population.

In a 2012 retrospective study in 9 Nordic transplant centers, 92 patients with MF in chronic phase underwent allo-HCT. MAC was given to 40 patients and RIC to 52 patients. Mean age in the 2 groups at transplantation was 46 and 55 years, respectively ($p<0.001$). When adjustment for age differences was made, survival of the patients treated with RIC was significantly better ($p=0.003$). Among the RIC patients, survival was significantly ($p=0.003$) greater for patients younger than age 60 years (a 10-year survival close to 80%) than for patients older than 60 years. The stem cell source did not significantly affect survival. No significant difference was found in NRM at 100 days between the MAC- and the RIC-treated patients. The probability of survival at 5 years was 49% for the MAC group and 59% in the RIC group ($p=0.125$). Patients treated with RIC experienced significantly less acute GVHD than in patients treated with MAC ($p<0.001$). The OS rates at 5 years were 70%, 59% and 41% for patients with Lille scores 0, 1, and 2, respectively ($p=0.038$, when adjusting for age). Furthermore, 21% of patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MAC-treated patients ($p<0.002$); 9% of patients needed a second transplant because of graft failure, disease progression, or transformation to AML, with no significant differences between groups.

Section Summary: Myeloproliferative Neoplasms

Observational studies of HCT for MPN have reported a range of 3- to 5-year OS rates from 35% to 50% and suggested that HCT may be associated with improved survival in patients with intermediate-2 and high-risk disease. Currently, only retrospective studies have compared the RIC and MAC regimens. While these nonrandomized comparisons have suggested that RIC may be used in patients who are older and who have poorer performance status without significantly worsening OS, randomized trials are needed to provide greater certainty in the efficacy of the conditioning regimens.

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SUMMARY OF EVIDENCE

For individuals who have MDS or MPN who receive MA conditioning allo-HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are 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 MF 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 RIC allo-HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Direct, prospective comparisons of outcomes after HCT with either MA conditioning or RIC in either MDS or MPN are not available. Evidence from retrospective, nonrandomized comparisons has suggested that RIC may be used in patients who are older and have more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of NRM but higher cancer relapse than MA 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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Policy History

Original Effective Date: 01/28/2002
 Current Effective Date: 06/20/2018

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

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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: 06/20/2018

- 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
- 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.

Next Scheduled Review Date: 06/2019

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 2017 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, 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-D46.1
	D46.20-D46.22 D46.4 D46.9 D46.A-D46.Z
	D47.1 D47.9 D47.Z1 D47.Z9

*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 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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