

<b>8.01.21 Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms</b>			
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<b>Section:</b>	11.0 Transplant	<b>Page:</b>	Page 1 of 25

## Policy Statement

Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be considered **medically necessary** as a treatment of **any** of the following diagnoses:

- I. Myelodysplastic syndromes (see Policy Guidelines section)
- II. Myeloproliferative neoplasms (see Policy Guidelines section)

Reduced-intensity conditioning (RIC) allo-HCT may be considered **medically necessary** as a risk-adapted treatment in patients who are at high risk of intolerance of a myeloablative conditioning regimen (see Policy Guidelines section), for **any** of the following diagnoses:

- I. Myelodysplastic syndromes
- II. Myeloproliferative neoplasms

Myeloablative allo-HCT or RIC allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that do not meet the criteria in the Policy Guidelines section is considered **investigational**.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## 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).

### 2016 WHO Classification Scheme for Myeloid Neoplasms and Acute Leukemia Myeloproliferative neoplasms (MPN)

- Chronic myeloid leukemia (CML), BCR-ABL1+
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera
- Primary myelofibrosis (PMF)
- Essential thrombocythemia
- Chronic eosinophilic leukemia, not otherwise specified
- MPN, unclassifiable
- Mastocytosis

### Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2

### Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL1-
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

### Myelodysplastic syndromes (MDS)

- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)

- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- *Provisional entity: refractory cytopenia of childhood*
- Myeloid neoplasms with germline predisposition

**Acute myeloid leukemia (AML) and related neoplasms**

**Blastic plasmacytoid dendritic cell neoplasm**

**Acute leukemias of ambiguous lineage**

**B-lymphoblastic leukemia/lymphoma**

**T-lymphoblastic leukemia/lymphoma**

**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 patients 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 patients are to improve quality of life and achieve transfusion independence. In the high-risk group, which includes intermediate-2 and high-risk IPSS groups, treatment goals are slowing disease progression to AML and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and  $\beta_2$ -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**

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

NA: not applicable.

**Table PG2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical**

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

AML: acute myelocytic leukemia.

An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS (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 5category IPSS to better characterize risk in MDS.

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

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for allo-HCT when chromosomal abnormalities are present, or when the disorder is associated with the development of significant cytopenias (e.g., neutrophils <500/mm<sup>3</sup>, platelets <20,000/mm<sup>3</sup>).

Patients 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 patients with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder. Use of allo-HCT should be based on the following criteria: cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some patients for whom a conventional myeloablative allo-HCT could be curative may be candidates for reduced intensity conditioning (RIC) allo-HCT. These include patients whose age (typically >60 years) or comorbidities (e.g., 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 patient, who usually share only 3 of the 6 major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease (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 patients of MAC-intolerance as follows:

- **Myelodysplastic Syndromes (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

## 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.

## Related Policies

- Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

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

### Background

#### 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 records the number of lineages in which dysplasia is seen (unilineage versus 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 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.<sup>1</sup> 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 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., U.S. 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 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup>

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. Cord blood transplantation is discussed in detail in Blue Shield of California Medical Policy: Placental and Umbilical Cord Blood as a Source of Stem Cells.

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 (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (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.

### **Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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**

#### **Clinical Context and Therapy Purpose**

The purpose of myeloablative or reduced-intensity conditioning allogeneic (RIC) hematopoietic cell transplant (allo-HCT) in patients who have myelodysplastic syndrome (MDS) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does myeloablative or RIC allo-HCT improve the net health outcome in patients with MDS?

The following PICO was used to select literature to inform this review.

#### **Populations**

The relevant population of interest is individuals with MDS.

#### **Interventions**

The therapies being considered are myeloablative or RIC allo-HCT.

## Comparators

The following therapies are currently being used: standard of care.

## Outcomes

The general outcomes of interest are mortality and morbidity. Beneficial outcomes are an improvement in overall survival (OS) and disease-specific survival. Harmful outcomes are treatment-related morbidity and mortality. Follow-up over months to years is of interest for relevant outcomes.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### 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.<sup>6</sup>

### Systematic Review

A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with myeloablative conditioning (MAC) for MDS.<sup>7</sup> Reviewers selected 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 cases (age range, 32 to 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, chronic myelomonocytic leukemia, myeloproliferative neoplasms, de novo and secondary acute myeloid leukemia (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 cyclophosphamide (CY) and CY plus total body irradiation, with cyclosporine A used for graft-versus-host disease (GVHD) prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Acute GVHD (grades II to IV) varied from 18% to 100%. Relapse risk ranged from 24% at 1 year to 36% at 5 years. The OS rates ranged from 25% at 2 years to 52% at 4 years, with nonrelapse mortality ranging from 19% at day 100 to 61% at 5 years.

A 2009 review from the American Society for Blood and Marrow Transplantation evaluated the evidence related to HCT in the therapy of MDS, with associated treatment recommendations.<sup>8</sup> Reviewers concluded that outcomes improved with early HCT for patients with an International Prognostic Scoring System (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).<sup>9</sup> 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 Allogeneic Hematopoietic Cell Transplantation Systematic Reviews

Song et al (2021) evaluated the efficacy of RIC followed by allo-HCT in patients with AML and MDS via a meta-analysis of 6 RCTs (N=1413).<sup>10</sup> The 6 RCTs compared RIC to MAC before first allo-HCT in patients with AML in complete remission or MDS, had a median follow-up of >1 year, and displayed a low risk of bias. The primary endpoint was OS. Results revealed that OS was not significantly different between RIC and MAC (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.64 to 1.4; p=.80), with combined long-term follow-up data also showing no difference in OS between the 2 conditioning approaches (HR, 0.86; 95% CI, 0.53 to 1.41; p=.56). The cumulative incidence of relapse was also similar between the groups (HR, 1.18; 95% CI, 0.88 to 1.49; p=.28). Nonrelapse mortality was significantly improved with RIC as compared to total body irradiation/busulfan-based MAC (HR, 0.53; 95% CI, 0.36 to 0.8; p=.002); however, treosulfan based MAC significantly reduced nonrelapse mortality as compared to RIC (HR, 1.67; 95% CI, 1.02 to 2.72; p=.04). RIC was associated with a trend of increasing graft failure (p=.06); however, graft failure in both arms was rare. The median duration of follow-up among the studies ranged from 12 to 119 months. The authors concluded that RIC is recommended as an adequate option of preparative treatment before allo-HCT for patients with AML in complete remission or MDS. Limitations of the meta-analysis included the small number of included clinical trials, significant heterogeneity between included studies for some outcomes, and lack of blinding in some studies.

## Randomized Controlled Trials

No published randomized trials have compared RIC plus allo-HCT with conventional chemotherapy alone in patients with MDS and AML for whom MAC chemotherapy and allo-HCT are contraindicated.

Three RCTs, all of which are included in the systematic review by Song et al (2021),<sup>10</sup> have compared r RIC and myeloablative regimens before allo-HCT in patients with MDS.<sup>11,12,13</sup> The RCTs are heterogeneous in patient characteristics and conditioning regimens and their findings vary based on these differences. In a long-term follow-up of one of the RCTs<sup>12</sup>, Scott et al (2021) found that, at 4 years, transplant-related mortality was significantly increased with MAC as compared to RIC (25.1% vs. 9.9%; p<.001) and those who received RIC had a significantly increased relapse risk (HR, 4.06; 95% CI, 2.59 to 6.35; p<.001).<sup>14</sup> Among those who relapsed after HCT, postrelapse survival was similar between groups at 3 years (24% for MAC vs. 26% for RIC). Patients administered MAC had superior OS (HR, 1.54; 95% CI, 1.07 to 2.2; p=.03).

Overall, findings from these RCTs appear consistent with the American Society for Blood and Marrow Transplantation's (2009) systematic review (previously described), which assessed the evidence supporting reduced-intensity and myeloablative conditioning 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."<sup>8</sup> Other reviews (2010 to 2012) have also drawn conclusions similar to those of the American Society for Blood and Marrow Transplantation.<sup>15-20</sup> Given the absence of curative therapies for these patients, RIC allo-HCT may be considered as a risk-adapted treatment strategy for patients with MDS who could benefit from allo-HCT but who are at high risk of MAC regimen intolerance.

## Noncomparative and Observational Studies

Additional nonrandomized evidence includes uncontrolled studies and prospective and retrospective cohort studies. Evidence from a number of largely heterogeneous, uncontrolled studies of r 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.<sup>7,21-31</sup> 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 cyclosporine A and tacrolimus used for GVHD prophylaxis. The reported incidence of grades II to IV GVHD was 9% to 63%, with a relapse risk of 6% to 61%. Rates of OS ranged between 44% at 1 year and 46% at 5 years (median follow-up range, 14 months to >4 years).

In general, nonrandomized studies of RIC compared to MAC showed a low rate of engraftment failure and low nonrelapse mortality with RIC, but a higher relapse rate than with MAC allo-HCT. Zeng et al (2014) conducted a systematic review and meta-analysis comparing outcomes for patients who had MDS or AML treated with HCT plus reduced intensity or myeloablative conditioning.<sup>32</sup> 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 the pooled analysis, OS, RFS, and nonrelapse mortality did not differ significantly between patients receiving reduced-intensity and myeloablative conditioning. Relapse incidence was significantly lower in the MAC arm (odds ratio [OR] for RIC vs. MAC, 1.41; 95% CI, 1.24 to 1.59;  $p < .001$ ).

Aoki et al (2015) compared RIC with MAC in a retrospective cohort of 448 patients (age range, 50 to 69 years) with advanced MDS (refractory anemia with excess blasts or refractory anemia in transformation).<sup>33</sup> Of the total, 197 (44%) and 251 (56%) received myeloablative or r RIC, respectively. The groups differed at baseline: patients who received r RIC were significantly more likely to be 60 to 69 years old (vs. 50 to 59 years; 47% for RIC vs. 47% for MAC;  $p = .001$ ), and less likely to receive an unrelated donor transplant (54% vs. 70%;  $p = .001$ ). Three-year OS rates did not differ between groups (44.1% for RIC vs. 42.7% for MAC;  $p = .330$ ). Although patients treated with RIC had a significantly lower 3-year cumulative incidence of nonrelapse mortality (25.6% vs. 37.9%;  $p = .002$ ), they had a significantly higher 3-year incidence of relapse than patients treated with MAC (29.9% vs. 22.8%;  $p = .029$ ).

Kim et al (2012) published a phase 3 randomized trial (N=83 patients) comparing toxicity rates for 2 conditioning regimens (reduced CY, fludarabine, and anti-thymocyte globulin; standard CY anti-thymocyte globulin).<sup>34</sup> 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%;  $p = .003$ ). Subgroup analyses showed no differences in the overall results based on differential diagnosis.

## Outcomes After Allogeneic Hematopoietic Cell Transplantation in Mixed Myelodysplastic Syndrome Populations

### Noncomparative and Observational Studies

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.

**Table 1. Case Series of Hematopoietic Cell Transplantation Treatment for Myelodysplastic Syndrome**

Study	Patient Population	Type of HCT	Summary of Outcomes
Basquiera et al (2015) <sup>35</sup>	52 pediatric patients with MDS	<ul style="list-style-type: none"> <li>• Allo-HCT (59% with related donors)</li> <li>• Stem cell source:                             <ul style="list-style-type: none"> <li>○ Bone marrow, 63%</li> <li>○ Peripheral blood, 26%</li> <li>○ Umbilical cord blood, 11%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• 5-y DFS=50%</li> <li>• 5-y OS=55%</li> </ul>

Study	Patient Population	Type of HCT	Summary of Outcomes
<b>Boehm et al (2014)<sup>36</sup></b>	60 adults with MDS or secondary AML	<ul style="list-style-type: none"> <li>• Allo-HCT</li> <li>• MAC in 36 patients; RIC in 24 patients</li> </ul>	10-y OS=46%
<b>Damaj et al (2014)<sup>37</sup></b>	128 adults with MDS: 40 received AZA before HCT and 88 received BSC	RIC allo-HCT	<ul style="list-style-type: none"> <li>• 3-y OS=53% in AZA group vs. 53% in BSC group (p=.69)</li> <li>• 3-y RFS=37% in AZA group vs. 42% in BSC group (p=.78)</li> <li>• 3-y NRM=20% in AZA group vs. 23% in BSC group (p=.74)</li> </ul>
<b>Di Stasi et al (2014)<sup>38</sup></b>	227 patients with MDS or AML	<ul style="list-style-type: none"> <li>• Allo-HCT</li> <li>• Donor source: <ul style="list-style-type: none"> <li>○ Matched-related, 38%</li> <li>○ Matched-unrelated, 48%</li> <li>○ Haploidentical, 14%</li> </ul> </li> </ul>	3-y PFS for patients in remission: <ul style="list-style-type: none"> <li>• 57% for matched-related</li> <li>• 45% for matched-unrelated</li> <li>• 41% for haploidentical (p=.417)</li> </ul>
<b>Onida et al (2014)<sup>39</sup></b>	<ul style="list-style-type: none"> <li>• 523 patients with MDS</li> <li>• IPSS cytogenetic risk group: <ul style="list-style-type: none"> <li>○ Good risk: 53.5%</li> <li>○ Intermediate risk: 24.5%</li> <li>○ Poor risk: 22%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Allo-HCT</li> <li>• RIC in 12%</li> </ul>	5-y OS based on IPSS cytogenetic risk group: <ul style="list-style-type: none"> <li>• Good: 48%</li> <li>• Intermediate: 45%</li> <li>• Poor: 30%</li> </ul>
Study	Patient Population	Type of HCT	Summary of Outcomes
<b>Oran et al (2014)<sup>40</sup></b>	<ul style="list-style-type: none"> <li>• 256 patients with MDS</li> <li>• Pretreatment: <ul style="list-style-type: none"> <li>○ No cytoreductive chemo: 30.5%</li> <li>○ Chemo: 15.6%</li> <li>○ HMA: 47.7%</li> <li>○ Chemo + HMA: 6.2%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Allo-HCT</li> <li>• RIC in 36.7%</li> </ul>	3-y EFS based on cytoreductive therapy: <ul style="list-style-type: none"> <li>• No cytoreductive chemo: 44.2%</li> <li>• Chemo: 30.6%</li> <li>• HMA: 34.2%</li> <li>• Chemo + HMA: 32.8% (p=.50)</li> </ul>
<b>Yoshimi et al (2014)<sup>41</sup></b>	17 children with secondary MDS or AML after childhood aplastic anemia	<ul style="list-style-type: none"> <li>• Allo-HCT</li> </ul>	5-y OS and EFS=41%

Study	Patient Population	Type of HCT	Summary of Outcomes
<b>Basquiera et al (2016)</b> <sup>42</sup>	<ul style="list-style-type: none"> <li>84 adults with MDS</li> <li>Cytogenetic risk group:                             <ul style="list-style-type: none"> <li>Standard: 65.5%</li> <li>Adverse: 12.6%</li> <li>Unknown: 21.9%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Allo-HCT</li> <li>RIC in 31.1%</li> </ul>	<p>OS:</p> <ul style="list-style-type: none"> <li>Median: 23.5 mo (95% CI, 1.7 to 45.3 mo)</li> <li>1-y=61% (95% CI, 50% to 70%)</li> <li>4-y=38% (95% CI, 27% to 49%)</li> </ul> <p>PFS:</p> <ul style="list-style-type: none"> <li>Median: 19.9 mo (95% CI, 9 to 31 mo)</li> <li>1-y=57% (95% CI, 46% to 67%)</li> <li>4-y=37% (95% CI, 26% to 48%)</li> </ul>
<b>Symeonidis et al (2015)</b> <sup>43</sup>	<ul style="list-style-type: none"> <li>513 adults with CMML</li> <li>Pretreatment:                             <ul style="list-style-type: none"> <li>No prior disease modifying therapy: 28%</li> <li>Disease modifying therapy: 72%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Allo-HCT</li> <li>RIC in 41.6%</li> </ul>	<ul style="list-style-type: none"> <li>1-y NRM=31%</li> <li>4-y NRM=41%</li> <li>4-y RFS=27%</li> <li>4-y OS=33%</li> </ul>
<b>Pohlen et al (2016)</b> <sup>44</sup>	<ul style="list-style-type: none"> <li>187 patients with refractory AML (87%) or high-risk MDS (13%)</li> </ul>	<ul style="list-style-type: none"> <li>Allo-HCT</li> <li>RIC in 52%</li> <li>Unrelated donors in 73%</li> <li>Stem cell source:                             <ul style="list-style-type: none"> <li>Bone marrow, 6%</li> <li>Peripheral blood, 94%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>3-y RFS=32% (95% CI, 25% to 39%)</li> <li>3-y OS=35% (95% CI, 27% to 42%)</li> </ul>
<b>Heidenreich et al (2017)</b> <sup>45</sup>	<ul style="list-style-type: none"> <li>313 adults with MDS and secondary AML, age ≥ 70</li> <li>Cytogenetic risk group:                             <ul style="list-style-type: none"> <li>Good: 51%</li> <li>Intermediate: 22%</li> <li>Poor/very poor: 11%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Allo-HCT</li> <li>RIC or non-MAC in 83%</li> <li>Unrelated donors in 75%</li> <li>Stem cell source:                             <ul style="list-style-type: none"> <li>Bone marrow, 6%</li> <li>Peripheral blood, 94%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>1-y NRM: 32%</li> <li>3-y relapse: 28%</li> <li>3-y OS: 34%</li> </ul>

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; EFS: event-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; PFS: progression-free survival; RFS: relapse-free survival; RIC: reduced-intensity conditioning.

### **Section Summary: Myelodysplastic Syndrome**

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. 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.

### **Myeloproliferative Neoplasms**

#### **Clinical Context and Therapy Purpose**

The purpose of MAC and RIC allo-HCT in patients who have myeloproliferative neoplasms is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does MAC or RIC allo-HCT improve the net health outcome in patients who have myeloproliferative neoplasms?

The following PICO was used to select literature to inform this review.

#### **Populations**

The relevant population of interest is individuals who have myeloproliferative neoplasms.

#### **Interventions**

The therapies being considered are MAC or RIC allo-HCT.

#### **Comparators**

The following therapies are currently being used: standard of care.

#### **Outcomes**

The general outcomes of interest are mortality and morbidity. Beneficial outcomes are an improvement in OS and disease-specific survival. Harmful outcomes are treatment-related morbidity and mortality. Follow-up over months to years is of interest for relevant outcomes.

#### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

#### **Review of Evidence**

Data on therapy for myeloproliferative neoplasms are sparse.<sup>28,46,47</sup> 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 myeloproliferative neoplasms.

#### **Systematic Reviews**

Bewersdorf et al (2021) assessed the available evidence on the efficacy and safety of allo-HCT in patients with myelofibrosis in a systematic review involving 43 studies (N=8739).<sup>48</sup> The analysis included 38 retrospective, 1 prospective, and 4 phase II clinical trials. Conditioning regimens used were variable with only 3 and 14 studies using exclusively MAC or RIC regimens,

respectively. Additionally, donor sources and pre-transplantation treatment histories differed considerably among studies. The co-primary outcome was 1-, 2-, and 5-year OS. Rates of nonrelapse mortality, RFS or progression-free survival (PFS), and safety were also evaluated. Regarding survival, 1-year, 2-year, and 5-year OS rates were 66.7% (95% CI, 63.5% to 69.8%), 64.4% (95% CI, 57.6% to 70.6%), and 55% (95% CI, 51.8% to 58.3%), respectively. Nonrelapse mortality rates for the same time periods were 25.9% (95% CI, 23.3% to 28.7%), 29.7% (95% CI, 24.5% to 35.4%), and 30.5% (95% CI, 25.9% to 35.5%). Rates of 1-, 2- and 5-year RFS were 65.3% (95% CI, 56.5% to 73.1%), 56.2% (95% CI, 41.6% to 69.8%), and 53.6% (95% CI, 39.9% to 66.9%), respectively. PFS rates were 56.9% (95% CI, 41.4% to 71.2%), 50.6% (95% CI, 39.7% to 61.4%), and 43.5% (95% CI, 31.9% to 55.8%) for these same time periods. Acute GVHD was reported in 44% of patients, with chronic GVHD occurring in 46.5% of patients. The combined rate of graft failure was 10.6% (95% CI, 8.9% to 12.5%). Overall, the quality of the evidence was limited by the absence of RCTs and the retrospective design of most studies. Additionally, patient and transplant characteristics were variable among the included studies leading to moderate to substantial heterogeneity in the analyses.

### Noncomparative and Observational Studies

The largest study identified evaluating allo-HCT for primary myelofibrosis 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.<sup>49</sup> Median age was 47 years (range, 18 to 73 years). Donors were human leukocyte antigen (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. Rates of DFS for patients receiving reduced-intensity conditioning allo-HCT were comparable: 39% for HLA identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic transplantation for myelofibrosis resulted in long-term RFS in about one-third of patients.

The significant toxicity of MAC plus allo-HCT in myeloproliferative neoplasms has led to study of r RIC regimens for these diseases. Data from a direct, prospective comparison of outcomes of MAC and allo-HCT versus RIC and allogeneic stem cell support in myeloproliferative neoplasms 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 myeloproliferative neoplasms who underwent allo-HCT using a r RIC regimen of low-dose (2 gray) total body irradiation alone with or without fludarabine.<sup>26</sup> At a median follow-up of 47 months, 3-year RFS was 37%, 3-year OS was 43%, and 3-year nonrelapse mortality was 32%.

A 2009 retrospective study analyzed the impact of conditioning intensity on outcomes for allo-HCT in patients with myelofibrosis.<sup>50</sup> 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 to 60 years) underwent MAC and 23 patients (median age, 54 years; range, 38 to 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 to 89 months), there was a trend for a better PFS rate at 3 years in RIC patients than in MAC patients (58% [range, 23% to 62%] vs. 43% [range, 35% to 76%], respectively;  $p=.11$ ); there was a similar trend in the 3-year OS rate (68% [range, 45% to 84%] vs. 48% [range, 27% to 66%], respectively;  $p=.08$ ). Nonrelapse mortality rates at 3 years trended higher in MAC cases (48%; range, 31% to 74%) than in r RIC cases (27%; range, 14% to 55%;  $p=.08$ ). The results of this study suggested that both types of conditioning regimens have curative potential in patients with myelofibrosis. 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.

### **Section Summary: Myeloproliferative Neoplasms**

Observational studies of HCT for myeloproliferative neoplasms 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. Primarily, retrospective studies have compared the RIC and MAC regimens. While these nonrandomized comparisons have suggested that reduced-intensity conditioning 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.

### **Summary of Evidence**

For individuals who have MDS who receive MAC or RIC allo- HCT, the evidence includes systemic reviews, RCTs, and numerous 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 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**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **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. 2.2022) make the following general recommendation about allogeneic hematopoietic cell transplantation (allo-HCT):<sup>51</sup>

"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 2.<sup>51</sup>

**Table 2. Guidelines for Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes**

Prognostic Category	Recommendations for Allo-HCT
<b>IPSS low/intermediate-1 OR IPSS-R very low, low, intermediate OR WPSS very low, low, intermediate</b>	<ul style="list-style-type: none"> <li>• Consider allo-HCT for select patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy</li> <li>• Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level &gt;500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy</li> </ul>
<b>IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high</b>	<ul style="list-style-type: none"> <li>• Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available</li> </ul>

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

Table 3 summarizes the National Comprehensive Cancer Network recommendations (v. 2.2021) on the use of allo-HCT for the treatment of myeloproliferative neoplasms.<sup>52</sup> 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 3. Guidelines for Allogeneic Hematopoietic Cell Transplantation for Myeloproliferative Neoplasms**

Prognostic Category	Recommendations for Allo-HCT
<b>Intermediate risk - 1 myelofibrosis IPSS=1 DIPSS-Plus=1 DIPSS=1 or 2</b>	<ul style="list-style-type: none"> <li>• Consider observation or ruxolitinib, peginterferon alfa-2a, or hydroxyurea if symptomatic (useful in certain circumstances) or allo-HCT</li> <li>• Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics</li> </ul>
<b>Intermediate risk - 2 myelofibrosis IPSS=2 DIPSS-Plus=2 or 3 DIPSS=3 or 4 High-risk myelofibrosis IPSS ≥3 DIPSS-Plus=4 to 6 DIPSS=5 or 6</b>	<ul style="list-style-type: none"> <li>• Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant</li> <li>• Evaluation for allo-HCT is recommended for all patients</li> </ul>
<b>Disease progression to advanced-stage/AML</b>	<ul style="list-style-type: none"> <li>• Induce remission with hypomethylating agents ± JAK inhibitors or intensive induction chemotherapy followed by allo-HCT</li> </ul>

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



### American Society of Transplantation and Cellular Therapy

In 2020, the American Society of Transplantation and Cellular Therapy (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.<sup>53</sup> Table 4 summarizes categorizations for allo-HCT in adults.

**Table 4. Recommendations for the Use of Hematopoietic Cell Transplantation to Treat Myelodysplastic Syndromes, Myelofibrosis, and Myeloproliferative Neoplasms**

Indication	Recommendation
<b>Myelodysplastic syndromes</b>	
<b>Low/intermediate-1 risk</b>	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")
<b>Intermediate-2/high-risk</b>	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
<b>Myelofibrosis and myeloproliferative neoplasms</b>	
<b>Primary, low-risk</b>	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
<b>Primary, intermediate/high-risk</b>	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
<b>Secondary</b>	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
<b>Hypereosinophilic syndromes, refractory</b>	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")

### 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),<sup>54</sup> 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
<b>Ongoing</b>			
NCT00739141	Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical Cord Blood in Patients with Hematologic Malignancies	86	Oct 2021
NCT01760655	Reduced Intensity Conditioning Before Donor Stem Cell Transplant in Treating Patients with High-Risk Hematologic Malignancies	72	Sep 2022
NCT02757989	Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk	79	Jun 2024

NCT: national clinical trial.

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## Documentation for Clinical Review

**Please provide the following documentation:**

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Specific transplant type being requested
  - Synopsis of alternative treatments performed and results
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history including comorbidities
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
  - Specific issues identified during the transplant evaluation
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
  - Chest x-ray (CXR)
  - PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
  - Cardiac echocardiogram
  - EKG
  - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
  - Bone marrow biopsy; Lymph node biopsy (as appropriate)
- Laboratory report(s)

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

Type	Code	Description
	38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
	38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
	38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
	38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
	38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
	38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	38230	Bone marrow harvesting for transplantation; allogeneic
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	86812	HLA typing; A, B, or C (e.g., A10, B7, B27), single antigen
	86813	HLA typing; A, B, or C, multiple antigens
	86816	HLA typing; DR/DQ, single antigen
	86817	HLA typing; DR/DQ, multiple antigens
86821	HLA typing; lymphocyte culture, mixed (MLC)	
<b>HCPCS</b>	S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and posttransplant care in the global definition

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
05/02/2014	Policy revision with position change
07/31/2015	Coding update
05/01/2016	Policy revision without position change
04/01/2017	Policy title change from Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms Policy revision without position change
07/01/2017	Coding update
01/01/2018	Coding update
03/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
04/01/2020	Annual review. Policy statement, guidelines and literature updated.
03/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.
04/01/2022	Annual review. Policy statement, guidelines and literature updated.



## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*



**Appendix A**

POLICY STATEMENT	
BEFORE <u>Red font: Verbiage removed</u>	AFTER <u>Blue font: Verbiage Changes/Additions</u>
<p><b>Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms 8.01.21</b></p> <p><b>Policy Statement:</b>                      Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be considered <b>medically necessary</b> as a treatment of <b>any</b> of the following diagnoses:</p> <ul style="list-style-type: none"> <li>I. Myelodysplastic syndromes (see Policy Guidelines section)</li> <li>II. Myeloproliferative neoplasms (see Policy Guidelines section)</li> </ul> <p>Reduced-intensity conditioning allo-HCT may be considered <b>medically necessary</b> as a risk-adapted treatment in patients who are at high-risk of intolerance of a myeloablative conditioning regimen (see Policy Guidelines section), for <b>any</b> of the following diagnoses:</p> <ul style="list-style-type: none"> <li>I. Myelodysplastic syndromes</li> <li>II. Myeloproliferative neoplasms</li> </ul> <p>Myeloablative allo-HCT or <u>reduced-intensity conditioning</u> allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that do not meet the criteria in the Policy Guidelines section is considered <b>investigational</b>.</p>	<p><b>Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms 8.01.21</b></p> <p><b>Policy Statement:</b>                      Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be considered <b>medically necessary</b> as a treatment of <b>any</b> of the following diagnoses:</p> <ul style="list-style-type: none"> <li>I. Myelodysplastic syndromes (see Policy Guidelines section)</li> <li>II. Myeloproliferative neoplasms (see Policy Guidelines section)</li> </ul> <p>Reduced-intensity conditioning (<u>RIC</u>) allo-HCT may be considered <b>medically necessary</b> as a risk-adapted treatment in patients who are at high risk of intolerance of a myeloablative conditioning regimen (see Policy Guidelines section), for <b>any</b> of the following diagnoses:</p> <ul style="list-style-type: none"> <li>I. Myelodysplastic syndromes</li> <li>II. Myeloproliferative neoplasms</li> </ul> <p>Myeloablative allo-HCT or <u>RIC</u> allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that do not meet the criteria in the Policy Guidelines section is considered <b>investigational</b>.</p>