Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Replaces N/A

Policy

Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be considered medically necessary as a treatment of

- Myelodysplastic syndromes (MDS) (see Policy Guidelines) OR
- Myeloproliferative neoplasms (MPN) (see Policy Guidelines).

Reduced-intensity conditioning allo-HCT may be considered medically necessary as a treatment of

- Myelodysplastic syndromes OR
- Myeloproliferative neoplasms in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. (see Policy Guidelines)

Myeloablative allo-HCT or reduced-intensity conditioning allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that does not meet the criteria in the Policy Guidelines is considered investigational.

Related Policies

7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells
8.01.15 Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
8.01.22 Allogeneic Hematopoietic Stem-Cell Transplantation for Genetic Diseases and Acquired Anemias
8.01.24 Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
8.01.25 Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
8.01.29 Hematopoietic Cell Transplantation for Hodgkin Lymphoma
8.01.511 Hematopoietic Cell Transplantation for Solid Tumors of Childhood
Policy Guidelines

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

2008 WHO Classification Scheme for Myeloid Neoplasms

- Acute myeloid leukemia
- Myelodysplastic syndromes (MDS)
- Myeloproliferative neoplasms (MPN)
  - Chronic myelogenous leukemia
  - Polycythemia vera
  - Essential thrombocythemia
  - Primary myelofibrosis
  - Chronic neutrophilic leukemia
  - Chronic eosinophilic leukemia, not otherwise categorized
  - Hypereosinophilic leukemia
  - Mast cell disease
  - MPNs, unclassifiable
- MDS/MPN
  - Chronic myelomonocytic leukemia
  - Juvenile myelomonocytic leukemia
  - Atypical chronic myeloid leukemia
  - MDS/MPN, unclassifiable
- Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
  - Myeloid neoplasms associate with PDGFRA rearrangement.
  - Myeloid neoplasms associate with PDGFRB rearrangement.
  - Myeloid neoplasms associate with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

2008 WHO Classification of MDS

- Refractory anemia (RA)
- RA with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- RCMD with ring sideroblasts
- RA with excess blasts 1 and 2 (RAEB 1 and 2)
- Del 5q syndrome
- Unclassified MDS

Risk Stratification of Myelodysplastic Syndromes

Risk stratification for MDS is performed using the IPSS. This system was developed after pooling data from 7 previous studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were built 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 divide patients into two categories: (1) low-risk and (2) high-risk groups. The low-risk group includes low-risk and Int-1 IPSS groups; the goals in low-risk MDS
patients are to improve quality of life and achieve transfusion independence. In the high-risk group—which includes Int-2 and high-risk IPSS groups—the goals are slowing the progression of disease to AML and improving survival. The IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and beta 2-microglobulin also should be considered after establishing the IPSS. If elevated, the prognostic category becomes worse by one category change.

Table PG 1. International Prognostic Scoring System: Myelodysplastic Syndrome
Prognostic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
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</thead>
<tbody>
<tr>
<td>Marrow blasts, %</td>
<td>&lt;5%</td>
<td>5%-10%</td>
<td>–</td>
<td>11%-20%</td>
<td>21%-30%</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td>–</td>
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Table PG2. International Prognostic Scoring System: Myelodysplastic Syndrome
Clinical Outcomes

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Total Score</th>
<th>Median Survival, y</th>
<th>Time for 25% to Progress to AML, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.12</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

AML: acute myelocytic leukemia.

In 2012, an updated 5-category IPSS was proposed prognosis in patients with primary MDS or secondary AML of to account for chromosomal abnormalities frequently seen in myelodysplastic syndromes. This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has been investigation of the possibility of using the 5-category IPSS to better characterize risk in MDS.

Given the long natural history of MDS, allo-HCT is typically considered in those with increasing numbers of blasts, signaling a possible transformation to acute myeloid leukemia. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for allo-HCT when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils <500/mm3, platelets <20,000/mm3).

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

Some patients for whom a conventional myeloablative allo-HCT could be curative may be considered candidates for RIC allo-HCT. These include those patients whose age (typically >60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one 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, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Clinical input suggests RIC allo-HCT may be considered for patients as follows:

- **MDS**
  - IPSS intermediate-2 or high risk
- RBC transfusion dependence
- Neutropenia
- Thrombocytopenia
- High-risk cytogenetics
- Increasing blast percentage

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

**Coding**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tbody>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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</table>

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
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<tbody>
<tr>
<td>S2150</td>
<td>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 post transplant care in the global definition</td>
</tr>
</tbody>
</table>

**Description**

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

For individuals who have MDS or MPN who receive myeloablative conditioning allo-HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. 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 overall survival of 40% to 50% are typical. For HCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis has demonstrated improved survival with HCT compared with standard therapy. HCT is at present the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS or MPN who receive reduced-intensity conditioning (RIC) allo-HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Direct, prospective comparisons of outcomes after HCT with either myeloablative 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 overall survival. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than myeloablative HCT. HCT is at present the only potentially curative treatment option for patients with MDSs and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Background**

**HCT**
Hematopoietic stem cells may be obtained from the transplant recipient (autologous hematopoietic cell transplantation [HCT]) or from a donor (allogeneic hematopoietic cell transplantation [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 “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in a separate policy. (see Related Policies)

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 a critical factor 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, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pre-transplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment 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.

RIC for Allo-HCT
RIC refers to the pre-transplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative (MA) conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM 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, 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, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully MA (conventional) regimens.

Myelodysplastic Syndromes
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 approximately 62% among individuals older than age 70 years. Patients either succumb to disease progression to acute myelocytic 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
For the past 20 years, the French-American-British (FAB) system has been used to classify MDS into 5 subtypes as follows: (1) refractory anemia (RA); (2) refractory anemia with ringed sideroblasts (RARS); (3) refractory anemia with excess blasts (RAEB); (4) refractory anemia with excess blasts in transformation; and, (5) chronic myelomonocytic leukemia. However, the FAB system has been 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% (see Policy Guidelines for WHO classification scheme for myeloid neoplasms).

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 (see Policy Guidelines). 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, such as peripheral blood counts or blast percentage. However, the IPSS has been useful in comparative analysis of clinical trial results and its utility confirmed at many institutions. 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 (WPSS) 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, however, is not yet in widespread use in clinical trials.

**MDS Treatment**
Treatment of smoldering or non-progressing MDS has in the past involved best supportive care including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. A diverse 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 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, eliminate the need for red blood cell transfusion, achieve complete remission, or 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.

**Chronic Myeloproliferative Neoplasms**
Myeloproliferative neoplasms (MPN) are clonal bone marrow stem-cell disorders; as a group, an approximate total of 8400 MPNs are diagnosed annually in the United States. Like MDS, MPNs primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older.

MPNs are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. They 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 mutations that affect protein tyrosine kinases or related molecules. The unifying characteristic common to all MPNs is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

**MPN Classification**
In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder with the term myeloproliferative neoplasms (MPN). These are a subdivision of myeloid neoplasms that includes the 4 classic disorders: chronic myeloid leukemia (CML), polycythemia vera, essential thrombocytopenia, and primary myelofibrosis; the WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, mast cell disease, and MPNs unclassifiable (see Policy Guidelines section).

**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
In November 2011, 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, spleen size, and symptoms of myelofibrosis when compared with placebo.(2) The COMFORT-II trial compared ruxolitinib to best available therapy in patients with intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS.(3) In a randomized trial comparing ruxolitinib with best available therapy, including antineoplastic agents, most commonly hydroxyurea, glucocorticoids, and no therapy, for myelofibrosis, Harrison et al demonstrated improvements in spleen size and quality of life, but not OS.(4)

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 effects of this procedure. However, the use of RIC of conditioning regimens for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

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.

Scope
Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application
N/A

Rationale
This policy was originally created in December 1999 and updated periodically with literature reviews, most recently through November 7, 2016. Following is the summary of the key literature to date.

Myelodysplastic Syndromes
Myeloablative Conditioning Allogeneic Hematopoietic Cell Transplantation Despite the successes seen with new drugs now available to treat myelodysplastic syndromes (MDS; e.g., decitabine, azacitidine, lenalidomide), allogeneic hematopoietic stem-cell transplantation (HCT) is the only treatment capable of complete and permanent eradication of the myelodysplastic syndrome (MDS) clone.(5)

A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with myeloablative (MA) conditioning for MDS.(6) The authors included 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1,378 cases with an age range of 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 (CML), MPNs, 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 cyclophosphamide (BU/CY) and CY plus total body irradiation (CY/TBI), with cyclosporine A (CYA) used for graft-versus-host disease (GVHD) prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Grades II to IV acute GVHD varied from 18% to 100%. Relapse risk ranged from a low of 24% at 1 year to 36% at 5 years. Overall survival (OS) ranged from 25% at 2 years to 52% at 4 years, with nonrelapse mortality (NRM) ranging from 19% at day 100 to 61% at 5 years.

A review from the American Society for Blood and Marrow Transplantation (ASBMT) in 2009 assembled and evaluated the evidence related to HCT in the therapy of MDS, with associated treatment recommendations. The authors conclude that outcomes are improved with early HCT for patients with an International Prognostic Scoring System (IPSS) score of intermediate-2 or high-risk at diagnosis, who have a suitable donor, and meet the transplant center’s eligibility criteria, and for selected patients with a low or intermediate-1 risk IPSS score at diagnosis who have a poor prognostic feature not included in the IPSS (i.e., older age, refractory cytopenias, etc.) Koebecki 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 acute myeloid leukemia (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 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 HCT for MDS**

Evidence from a number of largely heterogeneous, uncontrolled studies of reduced-intensity conditioning (RIC) with allo-HCT shows long-term remissions (i.e., longer than 4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with myelodysplastic syndromes/acute myelocytic leukemia (MDS/AML) who otherwise would not be candidates for MA conditioning regimens. These prospective and retrospective studies included cohorts of 16 to 215 patients similar to those in the MA 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%. The OS rates ranged between 44% at 1 year to 46% at 5 years, with a median follow-up range of 14 months to over 4 years.

Zeng et al (2014) conducted a systematic review and meta-analysis comparing outcomes for patients with MDS or AML treated with HCT with either RIC or MA conditioning. The review included 8 studies, 2 prospective and 8 retrospective, with a total of 6464 AML/MDS patients. A total of 171 received RIC and 4893 received MA conditioning. 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 MA conditioning. Relapse incidence was significantly lower in the MA conditioning arm (odds ratio for RIC vs MA conditioning, 1.41; 95% confidence interval [CI], 1.24 to 1.59; p<0.001).

Aoki et al compared RIC with MA conditioning in a retrospective cohort of 448 patients aged 50 to 69 years with advanced MDS (refractory anemia with excess blasts or refractory anemia in transformation). Of the total, 197 (44%) and 251 (56%) received MA conditioning 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 MA; p=0.001), and less likely to receive an unrelated donor transplant (54% vs 70%; p=0.001). Three-year OS did not differ between groups (44.1% for RIC vs 42.7% for MA; 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), but a significantly higher 3-year incidence of relapse than patients treated with MA conditioning (29.9% vs 22.8%; p=0.029).

In 2012, Kim et al. published a randomized Phase III trial to compare the toxicities of 2 different conditioning regimens (reduced cyclophosphamide [Cy], fludarabine, and antithymocyte globulin [ATG]; standard Cy-ATG). Four (of 83) patients had MDS, and the remaining study patients had severe aplastic anemia. Overall, the incidence of toxicities were reported to be lower in patients receiving the reduced-conditioning 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 at the cost of a higher relapse rate than with MA 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 MA and RIC regimens with allo-HCT. Furthermore, no randomized trials have been published in which RIC with allo-HCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom MA chemotherapy and allo-HCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, coupled with clinical input (see next), RIC allo-HCT may be considered medically necessary for patients with MDS who could benefit from allo-HCT but who for medical reasons (see Policy Guidelines) would be unable to tolerate a MA conditioning regimen.

The 2009 ASBMT systematic review previously described addressed the evidence to support RIC compared with MA conditioning regimens and makes 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.” (7)

Other recent reviews concur with the ASBMT recommendations. (23-28)

Outcomes after Allo-HCT in Mixed MDS Populations
A number of studies, primarily retrospective, continue to report outcomes from HCT for MDS in 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 HCT Treatment for MDS

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Type of HCT</th>
<th>Summary of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basquiera et al (2015)(29)</td>
<td>52 pediatric patients with MDS</td>
<td>Allo-HCT (59% with related donors)</td>
<td>5-y DFS: 50%</td>
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<tr>
<td></td>
<td></td>
<td>Stem cell source:</td>
<td>5-y OS: 55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Bone marrow, 63%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Peripheral blood, 26%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Umbilical cord blood, 11%</td>
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<tr>
<td>Boehm et al (2014)(30)</td>
<td>60 adults with MDS or secondary AML</td>
<td>Allo-HCT</td>
<td>10-y OS: 46%</td>
</tr>
<tr>
<td>Damaj et al (2014)(31)</td>
<td>128 adults with MDS, 40 of whom received AZA before HCT and 88 who received BSC</td>
<td>RIC allo-HCT</td>
<td>3-y OS: 53% in AZA group vs 53% in BSC group (p=0.69)</td>
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<td></td>
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<td>3-y RFS: 57% in AZA group vs 42% in BSC group (p=0.78)</td>
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<td></td>
<td>3-y NRM: 20% in AZA group vs 23% in BSC group (p=0.74)</td>
</tr>
<tr>
<td>Di Stasi et al (2014)(32)</td>
<td>227 patients with MDS or AML</td>
<td>Allo-HCT</td>
<td>3-y PFS for patients in remission:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Donor source:</td>
<td>57% for matched-related</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Matched-related, 38%</td>
<td>45% for matched-unrelated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Matched-unrelated, 48%</td>
<td>41% for haploidentical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Haploidentical, 14%</td>
<td>(p=0.417)</td>
</tr>
<tr>
<td>Onida et al (2014)(33)</td>
<td>523 patients with MDS treated with HCT</td>
<td>Allo-HCT</td>
<td>5-y OS based on IPSS cytogenic risk group:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPSS cytogenic risk group:</td>
<td>Good: 48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Good risk: 53.5%</td>
<td>Intermediate: 45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Intermediate risk: 24.5%</td>
<td>Poor: 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Poor risk: 22%</td>
<td></td>
</tr>
<tr>
<td>Oran et al (2014)(34)</td>
<td>256 patients with MDS</td>
<td>Allo-HCT</td>
<td>3-y EFS based on cytoreductive therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pretreatment:</td>
<td>No cytoreductive chemo: 44.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o No cytoreductive chemo: 30.5%</td>
<td>Chemo: 30.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Chemo: 15.6%</td>
<td>HMA: 34.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o HMA: 47.7%</td>
<td>Chemo + HMA: 32.8% (p=0.50)</td>
</tr>
<tr>
<td>Yoshimi et al (2014)(35)</td>
<td>17 children with secondary MDS or AML after childhood aplastic anemia</td>
<td>Allo-HCT</td>
<td>5-y OS and EFS: 41%</td>
</tr>
<tr>
<td>Basquiera et al</td>
<td>84 adults with MDS treated</td>
<td>Allo-HCT</td>
<td>OS:</td>
</tr>
</tbody>
</table>
Section Summary

Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of OS and progression-free survival (PFS) values, which reflects 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 MA conditioning 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 MA HCT.

Myeloproliferative Neoplasms (MPN)

Data on therapy for MPN remain sparse. As outlined previously in this policy, with the exception of MA chemotherapy and allo-HCT, no therapy has yet been proven to be curative or to prolong survival of patients with MPN.

The largest study identified of allo-HCT for primary myelofibrosis comes from analysis of the outcomes of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research (CIBMTR). The 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. DFS rates were 33%, 27%, and 22%, respectively. DFS for patients receiving reduced-intensity transplants was 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 relapse-free survival in about one-third of patients.
Gupta et al reported better DFS rates in a more recent analysis of 233 patients with primary myelofibrosis who underwent RIC HCT from 1997 to 2010. (43) Five-year OS was 47% (95% CI, 40% to 53%). Conditioning regimen was not significantly associated with OS.

In another relatively large study that included patients with primary myelofibrosis who were under 65 years old at diagnosis, Kroger et al compared outcomes for patients treated with allo-HCT (n=190) or conventional therapies (n=248) at diagnosis. (44) In the HCT group, 91 and 97 subjects received RIC and MA conditioning, respectively. Patients at low risk based on the Dynamic International Prognostic Scoring System 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 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 significantly differ in risk of death from those treated with conventional therapies. Although the study design is limited by the potential for bias due to patient selection, these results support using prognosis to guide decisions about HCT for primary myelofibrosis.

The significant toxicity of MA conditioning and allo-HCT in MPN has led to study of RIC regimens for these diseases. Data from direct, prospective comparison of outcomes of MA conditioning and allo-HCT versus RIC and autologous stem cell support in MPN are not available, but single arm series and nonrandomized comparative studies report outcomes after RIC allo-HCT. One series included 27 patients (mean age, 59 years) with MPN who underwent allo-HCT using an RIC regimen of low-dose (2 Gy) total body irradiation alone or with the addition of fludarabine. (14) At a median follow-up of 47 months, the 3-year relapse-free survival was 37%, and OS was 43%, with a 3-year NRM of 32%. In a second series, 103 patients (median age, 55 years; range, 32-68 years) with intermediate to high risk (86% of total patients) primary myelofibrosis or postessential thrombocythemia and polycythemia vera myelofibrosis were included on a prospective multicenter phase 2 trial to determine efficacy of a busulfan plus fludarabine-based RIC regimen followed by allo-HCT from related (n=33) or unrelated (n=70) donors. (45) Acute grade II-IV GVHD occurred in 27%, and chronic GVHD in 43% of patients. 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 versus 12% (95% CI, 5% to 19%) among cases with a matched donor (p=0.003). The cumulative relapse rate at 3 and 5 years was 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) 5-year estimated disease-free survival (DFS) and OS was 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 of allo-HCT in patients with myelofibrosis (MF). (46) 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 MA conditioning, 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 better PFS at 3 years in RIC patients compared with MA-conditioned patients (58%; range, 23-62 vs 43%; range, 35-76, respectively; p=0.11); there was a similar trend in 3-year OS (68%; range, 45-84 vs 48%; range, 27-66, respectively; p=0.08). NRM rates at 3 years trended higher in MA-conditioned cases than RIC cases (48%; range, 31-74 vs 27%; range, 14-55, respectively; p=0.06). The results of this study suggest 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 retrospective study in 9 Nordic transplant centers, a total of 92 patients with myelofibrosis in chronic phase underwent allo-HCT. (47) MA conditioning was given to 40 patients, and RIC was used in 52 patients. The mean age in the 2 groups at transplantation was 46±12 and 55±8 years, respectively (p<0.001). When adjustment for age differences was made, the 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 the survival. No significant difference was found in NRM at 100 days between the MA- and the RIC-treated patients. The probability of survival at 5 years was 49% for the MA-treated patients and 59% in the RIC group (p=0.125). Patients treated with RIC experienced significantly less acute GVHD compared with patients treated with MA conditioning (p<0.001). The OS at 5 years was 70%, 59% and 41% for patients with Lille score 0, 1, and 2, respectively (p=0.038, when age adjustment was made). Twenty-one percent of the patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MA-treated patients (p<0.002). Nine percent of the patients needed a second transplant because of graft failure, progressive disease or transformation to AML, with no significant difference between the groups.
**Section Summary**
Observational studies of HCT for MPN have reported a range of 3- to 5-year OS of 35% to 50% and suggested that HCT may be associated with improved survival in patients with intermediate-2 and high-risk disease. Direct comparisons between RIC and MA conditioning 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 who have poorer performance status without significantly worsening OS.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>NCT01366612</td>
<td>PRO#1278: A Phase III Study of Fludarabine and Busulfan Versus Fludarabine</td>
<td>54</td>
<td>Dec 2015 (ongoing)</td>
</tr>
<tr>
<td></td>
<td>and Busulfan and Low Dose Total Body Irradiation in Patients Receiving an</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Allogeneic Hematopoietic Stem Cell Transplant</td>
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<tr>
<td>NCT00739141</td>
<td>Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical</td>
<td>80</td>
<td>Aug 2017</td>
</tr>
<tr>
<td></td>
<td>Cord Blood in Patients with Hematologic Malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00176930</td>
<td>Allogeneic Transplant for Hematological Malignancy</td>
<td>350</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02581007</td>
<td>Reduced Intensity Conditioning and Transplantation of Partially HLA-</td>
<td>30</td>
<td>Feb 2018</td>
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<tr>
<td></td>
<td>Mismatched Peripheral Blood Stem Cells for Patients with Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00887068</td>
<td>Randomized Controlled Study of Post-transplant Azacitidine for Prevention</td>
<td>246</td>
<td>Apr 2018</td>
</tr>
<tr>
<td></td>
<td>of Acute Myelogenous Leukemia and Myelodysplastic Syndrome Relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01471444*</td>
<td>A Randomized Study of Once Daily Fludarabine-Clofarabine Versus Fludarabine</td>
<td>250</td>
<td>Nov 2018</td>
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<tr>
<td></td>
<td>Alone Combined With Intravenous Busulfan Followed by Allogeneic Hematopoietic Stem Cell Transplant for Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)</td>
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<tr>
<td>NCT00822393</td>
<td>Clinical Phase III Trial Treosulfan-Based Conditioning Versus Reduced-</td>
<td>960</td>
<td>Mar 2019</td>
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<tr>
<td></td>
<td>Intensity Conditioning (RIC) Prior to Allogeneic Hematopoietic Stem Cell</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Transplantation in Patients with AML or MDS Considered Ineligible to</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard Conditioning Regimens</td>
<td></td>
<td></td>
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<tr>
<td>NCT02626715</td>
<td>Reduced Intensity Conditioning (RIC) and Myeloablative Conditioning (MAC)</td>
<td>16</td>
<td>Sep 2019</td>
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<tr>
<td></td>
<td>for HCT in AML/MDS</td>
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<td></td>
</tr>
<tr>
<td>NCT01760655</td>
<td>Reduced Intensity Conditioning Before Donor Stem Cell Transplant in</td>
<td>50</td>
<td>Jan 2020</td>
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<tr>
<td></td>
<td>Treating Patients with High-Risk Hematologic Malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02757989</td>
<td>Allogeneic Hematopoietic Stem Cell Transplant in Patients with Myelodysplastic Syndrome Low Risk</td>
<td>105</td>
<td>Apr 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**
For individuals who have myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) who receive myeloablative conditioning allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. 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 overall survival of 40% to 50% are typical. For HCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis has demonstrated improved survival with HCT compared with
standard therapy. HCT is at present the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS or MPN who receive reduced-intensity conditioning (RIC) allo-HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Direct, prospective comparisons of outcomes after HCT with either myeloablative 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 overall survival. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than myeloablative HCT. HCT is at present the only potentially curative treatment option for patients with MDSs and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 academic medical center specialists prior to review for 2009. There was consensus among reviewers that reduced-intensity conditioning allogeneic hematopoietic cell transplantation (HCT) was of value in patients with myelodysplastic syndromes and myeloproliferative neoplasms who would be medically unable to tolerate a myeloablative HCT.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines
Current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myelodysplastic syndromes (MDS; v.2.2017) make the following recommendation about hematopoietic cell transplantation (HCT) in general(48):

“For patients who are transplant candidates, the first choice of a donor has remained an HLA [human leukocyte antigen]-matched sibling, although 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 NCCN guidelines related to HCT for MDS are outlined in Table 3.

Table 3: NCCN Guidelines for Allo-HCT for Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for HCT</th>
</tr>
</thead>
</table>
| IPSS low/intermediate-1 OR IPSS-R very low, low, intermediate OR WPSS very low, low, intermediate OR | **Consider allo-HCT for patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy**  
**Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy**  
**Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available** |
| IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high | **Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available** |

NCCN developed new guidelines for myeloproliferative neoplasms (MPN) in 2017 (v.2.2017). Table 3 summarizes the NCCN recommendations for the use of allogeneic HCT (allo-HCT) for the treatment of MPN. The guideline notes that selection of allo-HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.

**Table 4: NCCN Guidelines for Allo-HCT for Myeloproliferative Neoplasms**

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for Allo-HCT</th>
</tr>
</thead>
</table>
| Intermediate risk – 1 myelofibrosis  
 IPSS=1  
 DIPSS-Plus=1  
 DIPSS=1 or 2 | Consider observation or ruxolitinib if symptomatic or allo-HCT |
| 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 | Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant |
| Disease progression to advanced stage/AML | Induce remission with hypomethylating agents or intensive induction chemotherapy followed by allo-HCT |

**American Society for Blood and Marrow Transplantation**

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published guidelines on indications for HCT, based on the recommendations of a multiple-stakeholder task force. Autologous HCT was not generally recommended for MDS or MPS. ASBMT assigned the following categorizations to allo-HCT:

- **Myelodysplastic syndromes:**
  - Low/intermediate-1 risk: C
  - Intermediate-2/high risk: S
- **Myelofibrosis and myeloproliferative diseases:**
  - Primary, low risk: C
  - Primary, intermediate/high risk: C
  - Secondary: C
  - Hypereosinophilic syndromes, refractory: R

“S” indicates standard of care. The recommendation is “well defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies.” “C” indicates standard of care, clinical evidence available. Large clinical trials are not available; however, sufficiently large cohort studies have shown efficacy with “acceptable risk of morbidity and mortality.” “R” indicates 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.”

**European Blood and Marrow Transplantation Group and European LeukemiaNet**

In 2015, the European Blood and Marrow Transplantation and European LeukemiaNet Group published recommendations for the use of allo-HCT in primary myelofibrosis and for pre- and posttransplant management and donor selection. Recommendations related to the selection of patients for allo-HCT included:

- “All patients with intermediate-2 or high-risk disease according to IPSS, DIPSS [Dynamic International Prognostic Scoring System], or DIPSS+, and age < 70 years, should be considered potential candidates for allo-SCT [stem cell transplant].”
- “Patients with intermediate-1-risk disease and age <65 years should be considered candidates for allo-SCT if they present with either refractory, transfusion-dependent anemia or a percentage of blasts in PB [peripheral blood] >2%, or adverse cytogenetics (as defined by the DIPSS+ classification).”
- “Patients with low-risk disease should not undergo allo-SCT. They should be monitored and evaluated for transplantation when disease progression occurs.”
- “Patients in blast transformation (blasts in PB or in BM [bone marrow] or both equal to or >20%) are not
good candidates for allo-SCT. They should receive debulking therapy and be reconsidered for transplant after achieving a partial or complete remission of leukemia.”

- “Although the use of molecular risk classification for the identification of candidates for allo-SCT among intermediate-1 risk patients deserves further clinical validation, patients in this risk category who are triple negative (that is, JAKV617F, CALR, and MPL negative) or ASXL1 positive, or both, should be considered for allo-SCT.”

U.S. Preventive Services Task Force Recommendations
N/A

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


Appendix
<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/01/00</td>
<td>Add to Therapy Section - New Policy. Policy represents revision of 7.03.10 to focus on myelodysplasia and myelofibrosis. New policy statement on HDC for myelofibrosis.</td>
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<tr>
<td>11/12/02</td>
<td>Replace policy - Policy reviewed with no criteria changes.</td>
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<tr>
<td>07/13/04</td>
<td>Replace policy - Policy reviewed with literature; policy statement also now includes &quot;mini-transplant.&quot; References added; cross-reference to BC.8.01.38 on mini-transplants added.</td>
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<td>07/12/05</td>
<td>Replace policy - Policy reviewed with literature search; no change in policy statement. No further review scheduled.</td>
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<td>02/06/06</td>
<td>Codes updated - No other changes.</td>
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<td>06/02/06</td>
<td>Disclaimer and Scope Updates - No other changes.</td>
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<tr>
<td>10/09/07</td>
<td>Replace policy - Policy updated with literature review. Status changed from AR to BC. References added. No change in policy statement.</td>
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<tr>
<td>11/12/07</td>
<td>Codes updated - CPT code 86817 removed as directed by RPIW.</td>
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<td>05/13/08</td>
<td>Cross Reference Update - No other changes.</td>
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<td>03/10/09</td>
<td>Replace policy - Policy updated with literature search. Minor terminology changes to policy statements; the intent of the policy statements remain unchanged. Additional policy statements include Reduced intensity conditioning allogeneic SCT is considered investigational as a treatment of myeloproliferative disorders and myelodysplastic syndrome. References and codes added. &quot;High-Dose Chemotherapy&quot; removed from the title and throughout the body of the policy and &quot;myeloproliferative&quot; diseases added to the policy title.</td>
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<tr>
<td>12/08/09</td>
<td>Code Update - 86817 code added back to the policy.</td>
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<tr>
<td>02/09/10</td>
<td>Code Update - New 2010 codes added.</td>
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<tr>
<td>03/08/11</td>
<td>Replace policy - Policy updated with literature search, reference numbers 14-17 added. Myeloproliferative Disorders” replaced with “Myeloproliferative Neoplasms” in title and text. Policy statements revised to indicate that RIC HCT, previously investigational, may now be considered medically necessary as a treatment of myelodysplastic syndrome and myeloproliferative neoplasms in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Reviewed and recommended by OAP in February 2011.</td>
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<td>10/19/11</td>
<td>Related Policies updated; links refreshed.</td>
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<td>01/24/12</td>
<td>Code 38232 added.</td>
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<tr>
<td>02/09/12</td>
<td>CPT code 38204 was removed from the policy.</td>
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<tr>
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<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<td>01/29/13</td>
<td>Replace policy. Title revised with addition of the word “Hematopoietic”. Policy rationale updated based on a literature review through September 2012. Reference 26 added; others renumbered or removed. Policy statements unchanged.</td>
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<td>10/18/13</td>
<td>Update Related Policies. Change title to 8.01.17.</td>
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<td>01/21/14</td>
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<td>Update Related Policies. Add 8.01.15 and delete 8.01.514.</td>
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<td>04/18/14</td>
<td>Update Related Policies. Remove 8.01.20 and add 8.01.529.</td>
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<tr>
<td>06/24/14</td>
<td>Update Related Policies. Remove 8.01.35, 8.01.42 and 8.01.54, then add 8.01.530, 8.01.531 and 8.01.532.</td>
</tr>
<tr>
<td>12/03/14</td>
<td>Update Related Policies. Remove 8.01.21 and 8.01.26.</td>
</tr>
<tr>
<td>01/28/15</td>
<td>Annual Review. Policy updated with literature review through September 30, 2014. References 1-3, 5-6, 26-32, and 37 added. Policy statements unchanged. Remove ICD-9 and ICD-10 diagnosis codes; these are not utilized in policy adjudication.</td>
</tr>
</tbody>
</table>
02/19/15 Update Related Policies. Remove 8.01.30.
08/09/16 Update Related Policies. Remove 8.01.27 as it was archived.
09/30/16 Coding Update. Remove CPT 86817 from coding section.
11/04/16 Coding update. Removed codes that are transplant benefit related.
03/14/17 Annual review. Policy name changed to Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms. Policy updated with literature review through November 7, 2016; references 37-38 and 49-50 added. Changed “hematopoietic stem cell transplantation” to "hematopoietic cell transplantation" per NCCN terminology change. Policy statements unchanged.
08/01/17 Updated title of Related Policy 8.01.511.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.
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  - Qualified sign language interpreters
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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the OCR Portal at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S909, HH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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