Introduction

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) are diseases of bone marrow and the blood cells they produce. These disorders can turn into a certain type of leukemia (acute myelocytic leukemia, or AML). A type of treatment called a hematopoietic stem cell transplant is sometimes used to treat these conditions.
Hematopoietic stem cells are cells that are made within the bone marrow and can develop into many different types of blood cells. In a hematopoietic stem cell transplant, stem cells can be taken from a donor and transplanted into the person with the MDS or MPN. When the stem cells are harvested from a donor, it is called an allogeneic hematopoietic stem cell transplant.

This policy discusses when a hematopoietic stem cell transplant may be medically necessary to treat myelodysplastic syndromes and myeloproliferative neoplasms.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

### Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Myeloablative allogeneic hematopoietic cell transplantation** | Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be considered medically necessary as a treatment of:  
  - Myelodysplastic syndromes (MDS)  
  OR  
  - Myeloproliferative neoplasms (MPN)  
  
Myeloablative allo-HCT that does not meet the criteria above is considered investigational. |
| **Reduced-intensity conditioning allogeneic hematopoietic cell transplantation** | 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.  
  
Reduced-intensity conditioning allo-HCT that does not meet the criteria above is considered investigational. |
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
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 the disease to AML and improving survival. The IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and beta 2-microglobulin should also be considered after establishing the IPSS. If elevated, the prognostic category becomes worse by one category change.

### Table 1. International Prognostic Scoring System (IPSS): 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>
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<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Table 2. International Prognostic Scoring System (IPSS): 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>Risk Group</td>
<td>Total Score</td>
<td>Median Survival, y</td>
<td>Time for 25% to Progress to AML, y</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>-----------------------------------</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 for prognosis in patients with primary MDS or secondary AML 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. The possibility of using the 5-category IPSS to better characterize risk in MDS has also been investigated.

Given the long natural history of MDS, allo-HCT is typically considered in patients 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 (eg, 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 (eg, 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>Code</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>CPT</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<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</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>services; and the number of days of pre and post transplant care in the global definition</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

N/A

### Evidence Review

**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.

**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 "naive" 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 (eg, 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. These effects 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 (Reduced Intensity Conditioning) 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 the associated treatment-related morbidity and non-relapse mortality (NRM) after allogeneic transplantation. 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 their effects, from being nearly completely myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and the patient’s 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, 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 the Policy Coverage Criteria section 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. 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 has been 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**

In the past, treatment of smoldering or non-progressing MDS has 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 (eg, erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (eg, U.S. Food and Drug Administration [FDA]–approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (eg, lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (eg, cytarabine), and allo-HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront. That is to say, deciding whether the goal 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.

**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 that may evolve 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 Coverage Criteria 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 thrombocytosis and polycythemia vera and intermediate- and high-risk primary myelofibrosis.

In November 2011, the FDA approved the orally-administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis when compared with placebo. The COMFORT-II trial compared ruxolitinib to the best available therapy in patients with intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS. A 2012 randomized trial by Harrison et al compared ruxolitinib with the best available, most common treatments for myelofibrosis. The most common therapies were antineoplastic agents (most frequently hydroxyurea), glucocorticoids, and no therapy. Ruxolitinib demonstrated improvements in spleen size and quality of life, but not OS.

MA allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the procedure’s often severe treatment-related adverse effects. However, the use of RIC for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders.
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 MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
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<tr>
<td>NCT01366612</td>
<td>PRO#1278: A Phase III Study of Fludarabine and Busulfan Versus Fludarabine, Busulfan and Low Dose Total Body Irradiation in Patients Receiving an Allogeneic Hematopoietic Stem Cell Transplant</td>
<td>54</td>
<td>Dec 2015 (ongoing)</td>
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<tr>
<td>NCT00739141</td>
<td>Conditioning Regimen and the Transplantation of Unrelated Donor Umbilical Cord Blood in Patients with Hematologic Malignancies</td>
<td>80</td>
<td>Aug 2017</td>
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<tr>
<td>NCT00176930</td>
<td>Allogeneic Transplant for Hematological Malignancy</td>
<td>350</td>
<td>Dec 2017</td>
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<tr>
<td>NCT02581007</td>
<td>Reduced Intensity Conditioning and Transplantation of Partially HLA-Mismatched Peripheral Blood Stem Cells for Patients with Hematologic Malignancies</td>
<td>30</td>
<td>Feb 2018</td>
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<tr>
<td>NCT00887068</td>
<td>Randomized Controlled Study of Post-transplant Azacitidine for Prevention of Acute Myelogenous Leukemia and Myelodysplastic Syndrome Relapse</td>
<td>246</td>
<td>Apr 2018</td>
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<tr>
<td>NCT01471444a</td>
<td>A Randomized Study of Once Daily Fludarabine-Clofarabine Versus Fludarabine Alone Combined With Intravenous Busulfan Followed by Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)</td>
<td>250</td>
<td>Nov 2018</td>
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<tr>
<td>NCT00822393</td>
<td>Clinical Phase III Trial Treosulfan-Based Conditioning Versus Reduced-Intensity Conditioning (RIC) Prior to Allogeneic Hematopoietic Stem Cell Transplantation in Patients with AML or MDS Considered Ineligible to Standard Conditioning Regimens</td>
<td>960</td>
<td>Mar 2019</td>
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<tr>
<td>NCT02626715</td>
<td>Reduced Intensity Conditioning (RIC) and Myeloablative Conditioning (MAC) for HCT in AML/MDS</td>
<td>16</td>
<td>Sep 2019</td>
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<tr>
<td>NCT01760655</td>
<td>Reduced Intensity Conditioning Before Donor Stem Cell Transplant in Treating Patients with High-Risk Hematologic Malignancies</td>
<td>50</td>
<td>Jan 2020</td>
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<tr>
<td>NCT02757989</td>
<td>Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk</td>
<td>105</td>
<td>Apr 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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:

“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 4.

Table 4: NCCN Guidelines for Allo-HCT for Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS low/intermediate-1 OR IPSS-R very low, low, intermediate</td>
<td>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</td>
</tr>
</tbody>
</table>
OR WPSS very low, low, intermediate
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

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

Table 5: NCCN Guidelines for Allo-HCT for Myeloproliferative Neoplasms

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for Allo-HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk – 1 myelofibrosis</td>
<td>Consider observation or ruxolitinib if symptomatic or allo-HCT</td>
</tr>
<tr>
<td>IPSS=1</td>
<td></td>
</tr>
<tr>
<td>DIPSS-Plus=1</td>
<td></td>
</tr>
<tr>
<td>DIPSS=1 or 2</td>
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<tr>
<td>Intermediate risk – 2 myelofibrosis</td>
<td>Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant</td>
</tr>
<tr>
<td>IPSS=2</td>
<td></td>
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<tr>
<td>DIPSS-Plus=2 or 3</td>
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<tr>
<td>High-risk myelofibrosis</td>
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<tr>
<td>IPSS&gt;3</td>
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</tr>
<tr>
<td>DIPSS-Plus=4 to 6</td>
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</tr>
<tr>
<td>DIPSS=5 or 6</td>
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</tbody>
</table>


NCCN developed new guidelines for myeloproliferative neoplasms (MPN) in 2017 (v.2.2017).49 Table 5 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.
Prognostic Category | Recommendations for Allo-HCT
--- | ---
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.”

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.

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.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</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>
</tr>
<tr>
<td>11/12/02</td>
<td>Replace policy - Policy reviewed with no criteria changes.</td>
</tr>
<tr>
<td>07/13/04</td>
<td>Replace policy - Policy reviewed with literature; policy statement also now includes “mini-transplant.” References added; cross-reference to BC.8.01.38 on mini-transplants added.</td>
</tr>
<tr>
<td>07/12/05</td>
<td>Replace policy - Policy reviewed with literature search; no change in policy statement. No further review scheduled.</td>
</tr>
<tr>
<td>02/06/06</td>
<td>Codes updated - No other changes.</td>
</tr>
<tr>
<td>06/02/06</td>
<td>Disclaimer and Scope Updates - No other changes.</td>
</tr>
<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>
</tr>
<tr>
<td>11/12/07</td>
<td>Codes updated - CPT code 86817 removed as directed by RPIW.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>Cross Reference Update - No other changes</td>
</tr>
<tr>
<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. “High-Dose Chemotherapy” removed from the title and throughout the body of the policy and ”myeloproliferative” diseases added to the policy title.</td>
</tr>
<tr>
<td>12/08/09</td>
<td>Code Update - 86817 code added back to the policy.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Code Update - New 2010 codes added.</td>
</tr>
<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</td>
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<tr>
<td>10/19/11</td>
<td>Related Policies updated; links refreshed.</td>
</tr>
<tr>
<td>01/06/12</td>
<td>Replace policy – Policy updated with literature search; references 15-18 and 20 added. Policy statements unchanged. ICD-10 codes added.</td>
</tr>
<tr>
<td>01/24/12</td>
<td>Code 38232 added.</td>
</tr>
<tr>
<td>02/09/12</td>
<td>CPT code 38204 was removed from the policy.</td>
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<tr>
<td>06/20/12</td>
<td>Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.</td>
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<tr>
<td>08/01/12</td>
<td>Update Related Policies Titles: 8.01.17, 8.01.22, 8.01.30, 8.01.35, and 8.01.520. Removed Related Policy 8.01.38 as it was archived.</td>
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<tr>
<td>10/01/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<tr>
<td>01/29/13</td>
<td>Replace policy. Title revised with addition of the word &quot;Hematopoietic&quot;. 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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<tr>
<td>09/30/13</td>
<td>Update Related Policies. Change title to 8.01.31.</td>
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<tr>
<td>10/18/13</td>
<td>Update Related Policies. Change title to 8.01.17.</td>
</tr>
<tr>
<td>01/21/14</td>
<td>Replace policy. Policy updated with literature search through October 8, 2013; reference 14 added. Policy statements unchanged. CPT code 38230 removed from policy; it does not apply.</td>
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<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.30.</td>
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<tr>
<td>03/21/14</td>
<td>Update Related Policies. Add 8.01.15 and delete 8.01.514.</td>
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<tr>
<td>04/18/14</td>
<td>Update Related Policies. Remove 8.01.20 and add 8.01.529.</td>
</tr>
<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>
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<tr>
<td>12/03/14</td>
<td>Update Related Policies. Remove 8.01.21 and 8.01.26.</td>
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<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>
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<tr>
<td>02/19/15</td>
<td>Update Related Policies. Remove 8.01.30.</td>
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<td>09/01/16</td>
<td>Update Related Policies. Remove 8.01.27 as it was archived.</td>
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<tr>
<td>09/30/16</td>
<td>Coding Update. Remove CPT 86817 from coding section.</td>
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<tr>
<td>11/04/16</td>
<td>Coding update. Removed codes that are transplant benefit related.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Updated title of Related Policy 8.01.511.</td>
</tr>
<tr>
<td>11/10/17</td>
<td>Policy moved to new format, no changes to policy statement.</td>
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If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
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 Office for Civil Rights Complaint Portal, available 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 S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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