MEDICAL POLICY – 8.01.21

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

BCBSA Ref. Policy: 8.01.21
Effective Date: May 1, 2018
Last Revised: Sept. 1, 2018
Replaces: N/A

RELATED MEDICAL 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 Cell Transplantation for Genetic Diseases and Acquired Anemias
8.01.24 Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
8.01.25 Hematopoietic 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
8.01.520 Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
8.01.529 Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
8.01.530 Hematopoietic Cell Transplantation for Primary Amyloidosis
8.01.531 Hematopoietic Cell Transplantation for Waldenstrom Macroglobulinemia
8.01.532 Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

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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) |
| 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 |

Myeloid Neoplasms

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 (AML)
- Myelodysplastic syndromes (MDS)
- Myeloproliferative neoplasms (MPN)
  - Chronic myelogenous leukemia
  - Polycythemia vera
  - Essential thrombocytemia
  - 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 (see Table 1). This system was developed after pooling data from 7 studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to group patients into either low-risk and high-risk groups (see Table 2). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group, which includes intermediate-2 and high-risk IPSS groups, treatment goals are slowing disease progression to AML and improving survival. The IPSS is usually calculated at the time of diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β₂-microglobulin also should be considered after establishing the IPSS. If elevated, the prognostic category worsens by one category level.

Table 1. 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>
</tr>
</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>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

IPSS: International Prognostic Scoring System.

Table 2. 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4 years</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3 years</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.12 years</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.4</td>
<td>0.2 years</td>
</tr>
</tbody>
</table>

An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS (Schanz et al, 2012). This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has also been an investigation into using the 5-category IPSS to better characterize risk in MDS.

Given the long natural history of MDS, allo-HCT is typically considered in patients with increasing numbers of blasts, signaling a possible transformation to acute myeloid leukemia (AML). 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 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 the following criteria: cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some patients for whom a conventional myeloablative allo-HCT could be curative may be considered candidates for reduced-intensity conditioning (RIC) allo-HCT. They include 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 human leukocyte antigen (HLA)-identical siblings, matched at the HLA-A, B, and DR loci (6/6). 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. Most patients will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as 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
- Red blood cell (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>
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<tr>
<td><strong>CPT</strong>&lt;br&gt;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>

**HCPCS**
- S2150

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<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>

**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
Consideration of Age

In this policy, RIC allogeneic HSCT may be considered medically necessary as a treatment of MPNs in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regime. MPNs primarily occur in older individuals, with the majority of cases reported in patients aged 60 and older. HSCT is at present the only potentially curative therapy. Since direct, prospective clinical trials of outcomes are not available, clinical input was obtained. The clinical input supported the use of allogeneic HSCT using either a myeloablative or RIC regimens in patients when selection is guided by age and disease risk factors.

Evidence Review

Description

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

Background

**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 55-60 years, with an age-adjusted incidence of approximately 62% among individuals older than age 70 years. Patients succumb either 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

The French-American-British (FAB) system has been used to classify MDS into 5 subtypes: (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 (eg, peripheral blood counts, blast percentage). However, the IPSS has been useful in comparative analysis of clinical trial results and its utility confirmed at many institutions. An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS. This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has been an investigation into using the 5-category IPSS to better characterize risk in MDS. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO Classification-based Prognostic Scoring System (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 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. An array of therapies are now available to treat MDS, including hematopoietic growth factors (eg, erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (eg, U.S. Food and
Drug Administration [FDA]‒approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (eg, lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (eg, cytarabine), and allo-HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront whether it is to improve anemia, thrombocytopenia, or neutropenia, to eliminate the need for red blood cell transfusion; to achieve complete remission, or to cure the disease.

Allo-HCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient’s risk preference, and severity of MDS at presentation.

**Chronic Myeloproliferative Neoplasms**

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

MPN are characterized by the slow but progressive expansion of a clone of cells with the potential 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 neoplasm. MPN 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.
**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 thrombocythemia and polycythemia vera and intermediate- and high-risk primary myelofibrosis.

In 2011, the FDA approved the orally administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis when compared with placebo.² The COMFORT-II trial (2013) compared ruxolitinib with 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), with no therapy for treatment of myelofibrosis, Harrison et al (2012) reported improvements in spleen size and quality of life, but not OS.⁴

Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate often severe treatment-related adverse events of this procedure. However, the use of RIC for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

**Hematopoietic Cell Transplantation (HCT)**

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

Reduced Intensity Conditioning (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 and to minimize as much as possible the associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in their effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, and intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.
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. At present, HCT is the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS or MPN who receive 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. At present, HCT is the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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>
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<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, Busulfan and Low Dose Total Body Irradiation in Patients Receiving an Allogeneic Hematopoietic Stem Cell Transplant</td>
<td>54</td>
<td>Aug 2018</td>
</tr>
<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 2018</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>
</tr>
<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 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 while this policy was under review in 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.1.2018) 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: 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</td>
<td>• Consider allo-HCT for patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with</td>
</tr>
</tbody>
</table>
### Prognostic Category

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS-R very low, low, intermediate OR WPSS very low, low, intermediate</td>
<td>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 &gt;500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy</td>
</tr>
<tr>
<td>IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high</td>
<td>• Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available</td>
</tr>
</tbody>
</table>

### Prognostic Category

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Recommendations for HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk – 1 myelofibrosis</td>
<td>• Consider observation or ruxolitinib if symptomatic or allo-HCT • Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics</td>
</tr>
<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 • Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics</td>
</tr>
<tr>
<td>High-risk myelofibrosis</td>
<td>• Induce remission with hypomethylating agents or intensive induction chemotherapy followed by allo-HCT</td>
</tr>
</tbody>
</table>

NCCN developed new guidelines for myeloproliferative neoplasms (MPN) in 2017 (v.2.2017).\(^{49}\) Table 5 summarizes the NCCN recommendations (v.2.2018) on the use of allo-HCT for the treatment of myeloproliferative neoplasms (MPN).\(^{49}\) The guidelines note that selection of allo-HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.
**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. Table 6 summarizes categorizations for allo-HCT.

**Table 6. Recommendations for the Use of HCT to Treat Myelodysplastic Syndromes, Myelofibrosis, and Myeloproliferative Neoplasms**

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

**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-
posttransplant management and donor selection.$^51$ 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 a national coverage determination for stem cell transplantation (110.23; formerly 110.81),$^52$ portions of which are highlighted below:

**“B. Nationally Covered Indications**

**I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

a. …Treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,

b. …Treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

c. …Treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.
Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study.

d. Effective ... January 27, 2016, allogeneic HSCT for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma, and participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source....

e. Effective ... January 27, 2016, allogeneic HSCT for myelofibrosis (MF) is covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. All Medicare approved studies must use appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source....

f. Effective ... January 27, 2016, allogeneic HSCT for sickle cell disease (SCD) is covered by Medicare only for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical study...."

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 &quot;mini-transplant.&quot; References added; cross-reference to BC.8.01.38 on mini-transplants added.</td>
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<tr>
<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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<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>
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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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<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. &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>
</tr>
<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>
</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 and myeloproliferative neoplasms in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Reviewed and recommended</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>----------</td>
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</tr>
<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>
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<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>
</tr>
<tr>
<td>06/20/12</td>
<td>Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.</td>
</tr>
<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 “Hematopoietic”. Policy rationale updated based on a literature review through September 2012. Reference 26 added; others renumbered or removed. Policy statements unchanged.</td>
</tr>
<tr>
<td>09/30/13</td>
<td>Update Related Policies. Change title to 8.01.31.</td>
</tr>
<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>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Add 8.01.15 and delete 8.01.514.</td>
</tr>
<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>
</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>
<tr>
<td>02/19/15</td>
<td>Update Related Policies. Remove 8.01.30.</td>
</tr>
<tr>
<td>09/01/16</td>
<td>Update Related Policies. Remove 8.01.27 as it was archived.</td>
</tr>
<tr>
<td>09/30/16</td>
<td>Coding Update. Remove CPT 86817 from coding section.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</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>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references updated. Removed investigational policy statements.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Minor update. Re-added Consideration of Age information, which was inadvertently removed during a previous update.</td>
</tr>
</tbody>
</table>

**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). ©2018 Premera All Rights Reserved.

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  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
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  • Qualified interpreters
  • Information written in other languages

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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at 200 Independence Avenue SW, Room 509F, HHH Building
U.S. Department of Health and Human Services
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 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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