Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Policy # 00061
Original Effective Date: 01/28/2002
Current Effective Date: 04/19/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT) as a treatment of myelodysplastic syndrome (MDS) to be eligible for coverage when the patient selection criteria are met.

Patient Selection Criteria
Allogeneic hematopoietic cell transplantation (HCT) as a treatment of myelodysplastic syndrome (MDS) will be considered when any of the following criteria are met:

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

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT) as a treatment of myeloproliferative neoplasms (MPNs) to be eligible for coverage when the patient selection criteria are met.

Patient Selection Criteria
Allogeneic hematopoietic cell transplantation (HCT) as a treatment of myeloproliferative neoplasms (MPNs) will be considered when any of the following criteria are met:

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

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT) as a treatment of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs) to be eligible for coverage when the patient selection criteria are met.

Patient Selection Criteria
Allogeneic hematopoietic cell transplantation (HCT) as a treatment of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs) will be considered when any of the following criteria are met:

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

Based on review of available data, the Company may consider reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) as a treatment of myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPNs) in patients who for medical reasons would be unable to tolerate a myeloablative (MA) conditioning regimen to be eligible for coverage.

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

Patient Selection Criteria
Allogeneic hematopoietic cell transplantation (HCT) as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 will be considered when ANY of the following criteria are met:

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

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) as a treatment of myelodysplastic syndrome (MDS) and/or myeloproliferative neoplasms (MPNs) when patient selection criteria are not met to be investigational.*
Background/Overview
Myelodysplastic syndromes and MPNs refer to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia (AML). Allogeneic HCT has been proposed as a curative treatment option for patients with these disorders.

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of 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 Hematopoietic Stem-Cell Transplantation
The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide [Cy], busulfan) with or without total body irradiation (TBI) 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 pretransplant 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 allogeneic 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
Reduced-intensity conditioning refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose MA conditioning treatments. The goal of RIC is to reduce disease burden 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. Reduced-intensity conditioning 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 allogeneic 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 non-MA, as opposed to fully MA (conventional) regimens.

**MYELODYSPLASTIC SYNDROMES**

Myelodysplastic syndromes 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 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 was used to classify MDS into 5 subtypes as follows: (1) RA; (2) RARS; (3) RAEB; (4) RAEB in transformation; and, (5) CML. However, the FAB system was supplanted by that of the World Health Organization (WHO), which records the number of lineages in which dysplasia is seen (unilineage vs multilineage), separates the 5q-syndrome, and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20%.

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS), which groups patients into 1 of 4 prognostic categories based on the number of cytopenias, cytogenetic profile, and the percentage of blasts in the bone marrow. This system underweights the clinical importance of severe, life-threatening neutropenia and thrombocytopenia in therapeutic decisions and does not account for the rate of change in critical parameters (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 investigation into using the 5-category IPSS to better characterize risk in MDS. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO classification-based Prognostic Scoring System uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML. This system, however, is not yet in widespread use in clinical trials.

**MDS Treatment**

Treatment of nonprogressing 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,
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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 [ATG], cyclosporine A [CYA]), 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, eliminate the need for RBC 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

Chronic MPNs 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.

Myeloproliferative neoplasms 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 neoplasm. These are a subdivision of myeloid neoplasms that includes the 4 classic disorders: CML, PCV, essential thrombocytopenia, and PMF; the WHO classification also includes CNL, CEL/hypereosinophilic syndrome, MCD, 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 thrombocytosis and PCV and intermediate- and high-risk PMF.

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 (MF). Ruxolitinib has been associated with improved OS, spleen size, and symptoms of MF when compared with placebo. The COMFORT-II trial compared ruxolitinib to best available therapy in patients with intermediate- and high-risk MF, and demonstrated improvements in spleen volume and OS. In a randomized trial comparing ruxolitinib with best available therapy, including antineoplastic agents, most commonly hydroxyurea, glucocorticoids, and no therapy, for MF, Harrison et al demonstrated improvements in spleen size and quality of life, but not OS.
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Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often severe treatment-related adverse 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.

Rationale/Source
This policy has been updated regularly with literature reviews of the MEDLINE database, most recently through November 7, 2016. Following is a summary of the key literature to date.

MYELODYSPLASTIC SYNDROMES
Myeloablative Conditioning Allo-HCT
Despite the successes seen with new drugs now available to treat MDS (eg, decitabine, azacitidine, lenalidomide), allo-HCT is the only treatment capable of complete and permanent eradication of the MDS clone.

A 2009 review of HCT for MDS evaluated the evidence for allo-HCT with MA conditioning for MDS. Reviewers selected 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1378 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, 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 TBI, with CYA used for GVHD prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Acute GVHD (grades II-IV) varied from 18% to 100%. Relapse risk ranged from a low of 24% at 1 year to 36% at 5 years. Overall survival ranged from 25% at 2 years to 52% at 4 years, with NRM ranging from 19% at day 100 to 61% at 5 years.

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

Evidence from a number of largely heterogeneous, uncontrolled studies of RIC with allogeneic HSCT shows long-term remissions (i.e., longer than 4 years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with 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 allogeneic 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 RIC or MA conditioning. Reviewers included 8 studies (2 prospective, 8 retrospective), with a total of 6464 AML or MDS patients. Of these, 171 received RIC and 4893 received 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 (2015) compared RIC with MA conditioning in a retrospective cohort of 448 patients ages 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 they had 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 3 trial to compare the toxicities of 2 different conditioning regimens (reduced Cy, fludarabine, and 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 allogeneic HSCT. 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 allogeneic HSCT. Furthermore, no randomized trials have been published in which RIC with allogeneic HSCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom MA chemotherapy and allogeneic HSCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, coupled with clinical input (see next), RIC allogeneic HSCT may be considered medically necessary for patients with
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MDS who could benefit from allogeneic HSCT but who for medical reasons 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.”

Other recent reviews concur with the ASBMT recommendations.

Outcomes After Allo-HCT in Mixed MDS Populations
A number of studies, primarily retrospective, continue to report outcomes from allo-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>
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<tbody>
<tr>
<td>Basquiera et al</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>(2015)</td>
<td></td>
<td>• Stem cell source:</td>
<td>• 5-y OS: 55%</td>
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<tr>
<td></td>
<td></td>
<td>o Bone marrow, 63%</td>
<td></td>
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<td></td>
<td></td>
<td>o Peripheral blood, 26%</td>
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<td></td>
<td></td>
<td>o Umbilical cord blood, 11%</td>
<td></td>
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<tr>
<td>Boehm et al</td>
<td>60 adults with MDS or secondary AML</td>
<td>• Allo-HCT</td>
<td>10-y OS: 46%</td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td>• MA conditioning in 36 patients; RIC in 24 patients</td>
<td></td>
</tr>
<tr>
<td>Damaj et al</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>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td></td>
<td>• 3-y RFS: 37% in AZA group vs 42% in BSC group (p=0.78)</td>
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<tr>
<td></td>
<td></td>
<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</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>(2014)</td>
<td></td>
<td>• Donor source:</td>
<td>• 57% for matched-related</td>
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<tr>
<td></td>
<td></td>
<td>o Matched-related, 38%</td>
<td>• 45% for matched-unrelated</td>
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<tr>
<td></td>
<td></td>
<td>o Matched-unrelated, 48%</td>
<td>• 41% for haploidentical (p=0.417)</td>
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<tr>
<td></td>
<td></td>
<td>• Haploidentical, 14%</td>
<td></td>
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<tr>
<td>Onida et al</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>(2014)</td>
<td></td>
<td>• RIC in 12%</td>
<td>• Good: 48%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Intermediate: 45%</td>
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<td></td>
<td></td>
<td></td>
<td>• Poor: 30%</td>
</tr>
<tr>
<td>Study</td>
<td>Patient Population</td>
<td>Type of HCT</td>
<td>Summary of Outcomes</td>
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| Oran et al (2014)   | 256 patients with MDS                                                               | Allo-HCT                     | 3-y EFS based on cytoreductive therapy; 3-y EFS based on cytoreductive therapy:  
|                     | Pretreatment:                                                                       | RIC in 36.7%                | • No cytoreductive chemo: 44.2%  
|                     | o No cytoreductive chemo: 30.5%                                                      |                              | • Chemo: 30.6%  
|                     | o Chemo: 15.6%                                                                      |                              | • HMA: 34.2%  
|                     | o HMA: 47.7%                                                                       |                              | • Chemo + HMA: 32.8% (p=0.50) |
| Yoshimi et al       | 17 children with secondary MDS or AML after childhood aplastic anemia               | Allo-HCT                     | 5-y OS and EFS: 41%                                                                                                                                                                                                     |
| Basquiera et al (2016) | 84 adults with MDS treated with HCT                                               | Allo-HCT                     | OS: Median: 23.5 mo (95% CI, 1.7 to 45.3 mo)  
|                     | Cytogenic risk group:                                                               | RIC in 31.1%                | • 1-y: 61% (95% CI, 50% to 70%)  
|                     | o Standard: 65.5%                                                                  |                              | • 4-y: 38% (95% CI, 27% to 49%)  
|                     | o Adverse: 12.6%                                                                   |                              | PFS: Median: 19.9 mo (95% CI, 9 to 31 mo)  
|                     | o Unknown: 21.9%                                                                  |                              | • 1-y: 57% (95% CI, 46% to 67%)  
|                     |                                                                                   |                              | • 4-y: 37% (95% CI, 26% to 48%)  |
| Symeonidis et al    | 513 adults with CMML treated with HCT                                               | Allo-HCT                     | NRM:  
| (2015)              | Pretreatment:                                                                       | RIC in 41.6%                | • 1-y: 31%  
|                     | o No prior disease-modifying therapy: 28%                                            |                              | • 4-y: 41%  
|                     | o Disease-modifying therapy: 72%                                                    |                              | • 4-y RFS: 27%  
|                     |                                                                                   |                              | • 4-y OS: 33%  |
| Pohlen et al (2016) | 187 patients with refractory AML (87%) or high-risk MDS (13%)                     | Allo-HCT                     | RFS at 3 y: 32% (95% CI, 25% to 39%)  
|                     |                                                                                   | RIC in 52%                   | OS at 3 y: 35% (95% CI, 27% to 42%)  
|                     | Unrelated donors in 73%                                                             | Unrelated donors in 73%      |  
|                     |                                                                                   | Stem cell source:  
|                     | o Bone marrow, 6%                                                                  | Bone marrow, 6%  
|                     |                                                                                   | Peripheral blood, 94%  
| Heidenreich et al   | 313 adults with MDS and secondary AML, age ≥ 70 y treated with allo-HCT              | Allo-HCT                     | NRM at 1 y: 32%  
| (2016)              | Cytogenic risk group:                                                               | RIC or non-MA conditioning in 83% | Relapse at 3 y: 28%  
|                     | o Good: 51%                                                                        | Unrelated donors in 75%      | OS at 3 y: 34%  
|                     | o Intermediate: 22%                                                                | Stem cell source:  
|                     | o Poor/very poor: 11%                                                              | Bone marrow, 6%  
|                     |                                                                                   | Peripheral blood, 94%  

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

Section Summary: Myelodysplastic Syndromes
Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of OS and progression-free survival (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
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 of allo-HCT for PMF 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. Disease free survival (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 MF 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 PMF who underwent RIC HSCT from 1997 to 2010. 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 (2015) compared outcomes for patients treated with allo-HCT (n=190) or conventional therapies (n=248) at diagnosis. In the HCT group, 91 and 97 subjects received RIC and 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 differ significantly in risk of death from those treated with conventional therapies. Although the study
design was limited by the potential for bias due to patient selection, these results support using prognosis to guide decisions about HCT for 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 allogeneic stem cell support in MPN are not available, but single-arm series and nonrandomized comparative studies have reported outcomes after RIC allo-HCT. One 2008 series included 27 patients (mean age, 59 years) with MPN who underwent allo-HCT using an RIC regimen of low-dose (2 gray) total body irradiation alone with or without fludarabine. At a median follow-up of 47 months, 3-year RFS was 37%, 3-year OS was 43%, and 3-year NRM was 32%. In a second series, 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 in a prospective, multicenter, phase 2 trial to determine the efficacy of a busulfan plus fludarabine-based RIC regimen followed by allo-HCT from related (n=33) or unrelated (n=70) donors. Acute GVHD (grade II-IV) occurred in 27% of patients, and chronic GVHD in 43%. The cumulative incidence of NRM at 1 year in all patients was 16% (95% CI, 9% to 23%), but reached 38% (95% CI, 15% to 61%) among those with a mismatched donor versus 12% (95% CI, 5% to 19%) among cases with a matched donor (p=0.003). The cumulative relapse rates at 3 and 5 years were 22% (95% CI, 13% to 31%) and 29% (95% CI, 16% to 42%), respectively. After a median follow-up of 33 months (range, 12-76 months), 5-year estimated DFS and OS were 51% (95% CI, 38% to 64%) and 67% (95% CI, 55% to 79%), respectively.

A 2009 retrospective study analyzed the impact of conditioning intensity on outcomes of allo-HCT in patients with myelofibrosis. 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 than in 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 (48%; range, 31%-74%) than in RIC cases (27%; range, 14%-55%; p=0.08). The results of this study suggested that both types of conditioning regimens have curative potential in patients with myelofibrosis. Despite the RIC patients being significantly older with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allo-HCT in this population.

In a 2012 retrospective study in 9 Nordic transplant centers, 92 patients with myelofibrosis in chronic phase underwent allo-HCT. MA conditioning was given to 40 patients and RIC to 52 patients. Mean age in the 2 groups at transplantation was 46 and 55 years, respectively (p<0.001). When adjustment for age differences was made, survival of the patients treated with RIC was significantly better (p=0.003). Among the RIC patients, survival was significantly (p=0.003) greater for patients younger than age 60 years (a 10-year survival close to 80%) than for patients older than 60 years. The stem cell source did not significantly affect survival. No significant difference was found in NRM at 100 days between the MA- and the RIC-
treated patients. The probability of survival at 5 years was 49% for the MA-conditioning group and 59% in the RIC group (p=0.125). Patients treated with RIC experienced significantly less acute GVHD than in patients treated with MA conditioning (p<0.001). OS at 5 years was 70%, 59% and 41% for patients with Lille scores 0, 1, and 2, respectively (p=0.038, when adjusting for age). Twenty-one percent of 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 patients needed a second transplant because of graft failure, disease progression or transformation to AML, with no significant difference between the groups.

Section Summary: Myeloproliferative Neoplasms
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

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<td>NCT02581007</td>
<td>Reduced Intensity Conditioning and Transplantation of Partially HLA-Mismatched Peripheral Blood Stem Cells for Patients with Hematologic Malignancies</td>
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<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>
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<td>NCT01471444*</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>
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<td>NCT00822393</td>
<td>Clinical Phase III Trial Treosulfan-Based Conditioning Versus Reduced-Intensity Conditioning (RIC) Prior to Allogeneic Hematopoietic Stem Cell Transplantation in</td>
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Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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<td>NCT02757989</td>
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<td>Apr 2021</td>
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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 prior to review for 2009. There was consensus among reviewers that reduced-intensity conditioning allogeneic HCT was of value in patients with myelodysplastic syndromes and myeloproliferative neoplasms who would be medically unable to tolerate a myeloablative HCT.

Summary
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 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.
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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.

References

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01/28/2002 Managed Care Advisory Council approval
06/24/2002 Format revision. No substance change to policy.
07/06/2004 Medical Director review
07/26/2004 Managed Care Advisory Council approval
05/03/2005 Medical Director review
05/17/2005 Medical Policy Committee review. Coverage eligibility change; “HDC and autologous SCS as initial treatment (i.e., in lieu of an initial course of conventional chemotherapy) of poor-risk germ cell tumors, or as initial treatment of a first relapse (i.e., in lieu of a course of conventional chemotherapy) is investigational”.
05/23/2005 Managed Care Advisory Council approval
06/07/2006 Medical Director review
05/02/2007 Medical Director review
05/23/2007 Medical Policy Committee approval. No change to coverage eligibility.

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10/01/2008 Medical Director review
10/22/2008 Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009 Medical Policy Committee approval
12/16/2009 Medical Policy Implementation Committee approval. Title changed from “Allogeneic Stem Cell Transplantation of Myelodysplastic and Myeloproliferative Diseases” to “Allogeneic Stem Cell Transplantation of Myelodysplastic Syndromes and Myeloproliferative Neoplasms”. Added criteria to the coverage for the treatment of myelodysplastic syndromes. Added criteria to the coverage for the treatment of myeloproliferative neoplasms. Added coverage with criteria for treatment of both myelodysplastic syndromes and myeloproliferative neoplasms. Added reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation to be eligible for coverage.
12/01/2010 Medical Policy Committee review
12/08/2011 Medical Policy Committee review
12/06/2012 Medical Policy Committee review
12/19/2012 Medical Policy Implementation Committee approval. Added coverage with criteria for allogeneic hematopoietic stem-cell transplantation as a treatment of myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1.
03/04/2013 Coding updated
12/12/2013 Medical Policy Committee review
12/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/08/2015 Medical Policy Committee review
01/21/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
04/07/2016 Medical Policy Committee review
04/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Removed “stem” from stem-cell and added “hematopoietic” into the title. Updated background/rationale and references.

Next Scheduled Review Date: 04/2018

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Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is investigational will be based on a consideration of the following:
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  B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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     3. Reference to federal regulations.

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  A. In accordance with nationally accepted standards of medical practice;
  B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
  C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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