Medical Policy

Allogeneic Hematopoietic Cell transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Policy Number: 155
BCBSA Reference Number: 8.01.21
NCD/LCD: National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)

Related Policies
- Placental and Umbilical Cord Blood as a Source of Stem Cells, #285
- Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, #150
- Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, #212

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be MEDICALLY NECESSARY as a treatment of:

- Myelodysplastic syndromes or
- Myeloproliferative neoplasms.

Reduced-intensity conditioning allo-HCT may be 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.

All other applications of allogeneic hematopoietic cell transplantation (HCT) as a treatment of myelodysplastic syndromes or myeloproliferative neoplasms are INVESTIGATIONAL.

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

2008 WHO Classification Scheme for Myeloid Neoplasms
1. Acute myeloid leukemia
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
   3.1 Chronic myelogenous leukemia
   3.2 Polycythemia vera
   3.3 Essential thrombocytopenia
   3.4 Primary myelofibrosis
   3.5 Chronic neutrophilic leukemia
   3.6 Chronic eosinophilic leukemia, not otherwise categorized
   3.7 Hypereosinophilic leukemia
   3.8 Mast cell disease
   3.9 MPNs, unclassifiable
4. MDS/MPN
   4.1 Chronic myelomonocytic leukemia
   4.2 Juvenile myelomonocytic leukemia
   4.3 Atypical chronic myeloid leukemia
   4.4 MDS/MPN, unclassifiable
5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1
   5.1 Myeloid neoplasms associated with PDGFRα rearrangement
   5.2 Myeloid neoplasms associated with PDGFRβ rearrangement
   5.3 Myeloid neoplasms associated with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

2008 WHO Classification of MDS
1. Refractory anemia (RA)
2. RA with ring sideroblasts (RARS)
3. Refractory cytopenia with multilineage dysplasia (RCMD)
4. RCMD with ring sideroblasts
5. RA with excess blasts 1 and 2 (RAEB 1 and 2)
6. del 5q syndrome
7. unclassified MDS

Risk Stratification of MDS
Risk stratification for MDS is performed using the IPSS (see Table PG1). This system was developed after pooling data from 7 studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were built based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to divide patients into 2 categories: (1) low-risk and (2) high-risk groups (see Table PG2). The low-risk group includes low-risk and Int-1 IPSS groups; the goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group—which includes intermediate-2 and highrisk IPSS groups—the goals are slowing the progression of disease to acute myeloid leukemia (AML) and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β2-microglobulin also should be considered after establishing IPSS. If elevated, the prognostic category becomes worse by 1 category change.

<table>
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<tbody>
<tr>
<td>Marrow blasts, %</td>
<td>&lt;5%</td>
<td>5%-10%</td>
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<td>11%-20%</td>
<td>21%-30%</td>
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<tr>
<td>Karyotype</td>
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<td>Poor</td>
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<td>Risk Group</td>
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<td>Median Survival, y</td>
<td>Time for 25% to Progress to AML, y</td>
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<td>---------------</td>
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<td>High</td>
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<td>0.4</td>
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</table>

AML: acute myelocytic leukemia.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

**Allogeneic HSCT for myelofibrosis (MF)**

Effective for claims with dates of service on or after 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.

A prospective clinical study seeking Medicare coverage for allogeneic HSCT for myelofibrosis pursuant to Coverage with Evidence Development (CED) must address the following question:

Compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with MF who receive allogeneic HSCT transplantation have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- (optional) Quality of life?

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population:

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.

b. The rationale for the study is well supported by available scientific and medical evidence.

c. The study results are not anticipated to unjustifiably duplicate existing knowledge.

d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.

e. The study is sponsored by an organization or individual capable of completing it successfully.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.

g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.

i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study’s primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessible manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).

l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Facilities must submit the required transplant essential data to the Stem Cell Therapeutics Outcomes Database.

**National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)**


**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.

No indicates that prior authorization is not required.

N/A indicates that this service is primarily performed in an inpatient setting.

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<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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</tr>
<tr>
<td>Medicare PPO BlueSM</td>
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**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.
The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
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</table>

### HCPCS Codes

<table>
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<tr>
<th>HCPCS codes</th>
<th>Code Description</th>
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<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)</td>
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### ICD-9 Procedure Codes

<table>
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<th>ICD-9-CM procedure codes</th>
<th>Code Description</th>
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<tr>
<td>41.05</td>
<td>Allogeneic hematopoietic stem cell transplant without purging</td>
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<tr>
<td>41.06</td>
<td>Cord blood stem cell transplant</td>
</tr>
<tr>
<td>41.08</td>
<td>Allogeneic hematopoietic stem cell transplant with purging</td>
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### ICD-10 Procedure Codes

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<td>Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
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<td>30233X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y1</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
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<tr>
<td>30243Y1</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30263G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach</td>
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<td>30263X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach</td>
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<tr>
<td>30263Y1</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach</td>
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Description

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic stem cells may be obtained from the transplant recipient (autologous hematopoietic cell transplantation [HCT]) or from a donor (allogeneic hematopoietic cell transplantation [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy #285.

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 of 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 preengraftment 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 for Allo-HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant 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 associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40% to 60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 60 years, with an age-
adjusted incidence of 62% among individuals older than age 70 years. Patients either succumb to
disease progression to acute myeloid leukemia (AML) or to complications of pancytopenias. Patients with
higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML
than do other patients.

MDS Classification and Prognosis
The French-American-British (FAB) system was used to classify MDS into 5 subtypes as follows: (1) refractory anemia; (2) refractory anemia with ringed sideroblasts; (3) refractory anemia with excess blasts; (4) refractory anemia with excess blasts in transformation; and (5) chronic myelomonocytic leukemia. The 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 requires. 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 involved best supportive care, including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. A diverse array of therapies are now available to treat MDS, including hematopoietic growth factors (eg, erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (eg, U.S. Food and Drug Administration [FDA]-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (eg, lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (eg, cytarabine), and allo-HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront whether it is to improve anemia, thrombocytopenia, or neutropenia, to eliminate the need for RBC 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.

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

In 2008, the WHO classification scheme replaced the term chronic myeloproliferative disorder with the term myeloproliferative neoplasm. MPNs are a subdivision of myeloid neoplasms that includes 4 classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocytenia, and primary myelofibrosis. The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, mast cell disease, and MPN 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 thrombocytenia and polycythemia vera, and intermediate- and high-risk primary myelofibrosis.

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

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

Summary

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. Allogeneic hematopoietic cell transplantation (allo-HCT) has been proposed as a curative treatment option for patients with these disorders.

For individuals who have MDS or MPN who receive myeloablative conditioning allo-HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Primarily uncontrolled, observational studies of HCT for MDS have reported a relatively large range of overall and progression-free survival rates, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year overall survival of 40% to 50% are typical. For HCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis has demonstrated improved survival with HCT compared with standard therapy. HCT is at present the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS or MPN who receive reduced-intensity conditioning (RIC) allo-HCT, the evidence includes primarily retrospective observational series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Direct, prospective comparisons of outcomes after HCT with either myeloablative conditioning or RIC in either MDS or MPN are not available. Evidence from retrospective nonrandomized comparisons has suggested that RIC may be used in patients who are older and have more comorbidities without significantly worsening overall survival.

RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than myeloablative HCT. HCT is at present the only potentially curative treatment option for patients with
MDSs and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Policy History**

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<th>Date</th>
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<tr>
<td>3/2017</td>
<td>BCBSA National medical policy review. Title changed. New references added. 3/2017</td>
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<tr>
<td>12/2016</td>
<td>Coverage clarified for Medicare Advantage based on National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23). 12/14/2016</td>
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<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>12/2012</td>
<td>Updated to add new CPT code 38243. Mikegsa.</td>
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<tr>
<td>1/1/2010</td>
<td>Medical policy 155 effective 1/1/2010 describing covered and non-covered indications.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**