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MEDICAL POLICY – 8.01.539

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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RELATED MEDICAL POLICIES:

8.01.15	Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
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
8.01.42	Hematopoietic Cell Transplantation for Primary Amyloidosis
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
8.01.531	Hematopoietic Cell Transplantation for Waldenström 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

Treatment	Medical Necessity
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 (RIC) allo-HCT may be considered medically necessary as a risk-adapted treatment of:** • Myelodysplastic syndromes **OR** • Myeloproliferative neoplasms in individuals who are at high-risk of intolerance of a myeloablative conditioning regimen

Myeloid Neoplasms

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

2022 WHO Classification Scheme for Myeloid Neoplasm and Histiocytic/Dendritic Neoplasms
Clonal hematopoiesis (CH)
• CH of indeterminate potential (CHIP)

2022 WHO Classification Scheme for Myeloid Neoplasm and Histiocytic/Dendritic Neoplasms

- Clonal cytopenia of undetermined significance (CCUS)

Myeloproliferative neoplasms (MPN)

- Chronic eosinophilic leukemia, not otherwise specified
- Chronic myeloid leukemia (CML), BCR-ABL1+
- Chronic neutrophilic leukemia (CNL)
- Essential thrombocythemia
- Juvenile myelomonocytic leukemia
- MPN, not otherwise specified
- Polycythemia vera
- Primary myelofibrosis (PMF)

Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell sarcoma

Childhood MDS

- Childhood MDS with low blasts
  - Hypocellular
  - Not otherwise specified
- Childhood MDS with increased blasts

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- MDS/MPN with neutrophilia
- MDS/MPN with SF3B1 mutation and thrombocytosis
- MDS/MPN, not otherwise specified

Myelodysplastic syndromes (MDS)

- MDS with defining genetic abnormalities
  - MDS with low blasts and isolated 5q deletion (MDS-5q)
  - MDS with low blasts and SF3B1 mutation (MDS-SF3B1), or MDS with low blasts and ring sideroblasts
  - MDS with biallelic TP53 inactivation (MDS-biTP53)

2022 WHO Classification Scheme for Myeloid Neoplasm and Histiocytic/Dendritic Neoplasms

- MDS, morphologically defined
  - MDS with low blasts (MDS-LB)
  - MDS, hypoplastic (MDS-h)
  - MDs with increased blasts (MDS-IB)
    - MDS-IB1
    - MDS-IB2
    - MDS with fibrosis (MDS-f)

Acute myeloid leukemia (AML)

- AML with defining genetic abnormalities
- AML, defined by differentiation

Secondary myeloid neoplasms

- Myeloid neoplasms post cytotoxic therapy
- Myeloid neoplasms associated with germline predisposition

Dendritic cell and histiocytic neoplasms

- Plasmacytoid dendritic cell neoplasms
- Langerhans cell and other dendritic cell neoplasms
- Histiocytic neoplasms

Acute leukemias of ambiguous lineage (ALAL)

- ALAL with defining genetic abnormalities
- ALAL, immunophenotypically defined

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 seven 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 individuals 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 individuals 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 on

diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β_2-microglobulin also should be considered after establishing the IPSS. If elevated, the prognostic category worsens by one category level.

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

Variable	0	0.5	1.0	1.5	2.0
Marrow blasts, %	<5%	5%-10%	N/A	11%-20%	21%-30%
Karyotype	Good	Intermediate	Poor	N/A	N/A
Cytopenias	0/1	2/3	N/A	N/A	N/A

N/A: not applicable.

Table 2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical Outcomes

Risk Group	Total Score	Median Survival, y	Time for 25% of patients to Progress to AML
Low	0	5.7	9.4 years
Intermediate-1	0.5-1.0	3.5	3.3 years
Intermediate-2	1.5-2.0	1.2	1.12 years
High	≥2.5	0.4	0.2 years

AML: acute myelocytic leukemia.

An updated 5-category IPSS has been proposed for prognosis in individuals with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS. This system stratifies individuals 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, allogeneic hematopoietic cell transplantation (allo-HCT) is typically considered in individuals with increasing numbers of blasts, signaling a possible transformation to AML. Subtypes falling into this category include refractory anemia with excess

blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia (CMML).

Individuals with refractory anemia with or without ringed sideroblasts may be considered candidates for allo-HCT when chromosomal abnormalities are present, or when the disorder is associated with the development of significant cytopenias (e.g., neutrophils <500/mm^3, platelets <20,000/mm^3).

Individuals with myeloproliferative neoplasms 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 individuals with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder. Use of allo-HCT should be based on the following criteria: cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some individuals for whom a conventional myeloablative allo-HCT could be curative may be candidates for reduced-intensity conditioning (RIC) allo-HCT. They include individuals whose age (typically >60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude the 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 individual, who usually there is share only 3 of the 6 major histocompatibility antigens. Most individuals 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 GVHD extensive as that with matched donors.

Evidence and clinical guidelines suggest RIC allo-HCT may be considered as a risk-adapted strategy for high-risk individuals of MAC-intolerance as follows:

MDS

- Older age
- IPSS intermediate-2 or high risk
- Multiple comorbidities (e.g., hematopoietic cell transplantation-comorbidity index (HCT-CI) score higher than 2)
- Red blood cell (RBC) transfusion dependence

- Neutropenia
- Thrombocytopenia
- High-risk cytogenetics
- Increasing blast percentage

Myeloproliferative Neoplasm

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

Documentation Requirements
The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of: • Diagnosis/condition • History and physical examination documenting the severity of the condition • Whether myeloablative or reduced intensity conditioning allo-HCT is planned • Contraindications to myeloablative conditioning regimen, if applicable

Coding

Code	Description
CPT	
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
HCPCS	
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis

Code	Description
	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

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 HCT may be considered medically necessary as a treatment of MPNs in individuals 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 individuals aged 60 and older. HCT 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 HCT using either a myeloablative or RIC regimens in individuals when selection is guided by age and disease risk factors.

Evidence Review

Description

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms 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 individuals 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 insults. Chromosomal abnormalities are seen in 40% to 60% of individuals, 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 62% among individuals older than age 70 years. Individuals succumb either to disease progression to AML or to complications of pancytopenias. Individuals with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other individuals.

Myelodysplastic Syndrome Classification and Prognosis

The French-American-British system was used to classify MDS into five subtypes: (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 French-American-British system was supplanted by that of the World Health Organization (WHO), which records the number of lineages in which dysplasia is seen (unilineage versus 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).[1]

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS), which groups individuals into one of four 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 (e.g., 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 individuals with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS.[2] This system stratifies individuals into five 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 uses a 6-

category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML.

Myelodysplastic Syndrome Treatment

Treatment of non-progressing MDS has involved best supportive care, including red blood cell 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 (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., US Food and Drug Administration (FDA) approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic hematopoietic cell transplantation (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 individual age, performance status, medical comorbidities, the individual's risk preference, and severity of MDS at presentation. Allo-HCT is discussed in more detail in a subsequent section.

Chronic Myeloproliferative Neoplasms

Chronic myeloproliferative neoplasms are clonal bone marrow stem-cell disorders; as a group, approximately 8,400 myeloproliferative neoplasms are diagnosed annually in the United States. Like MDS, myeloproliferative neoplasms primarily occur in older individuals, with approximately 67% reported in individuals aged 60 years and older.

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

Myeloproliferative Neoplasm Classification

Myeloproliferative neoplasms are a subdivision of myeloid neoplasms that includes four classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia not otherwise specified, and myeloproliferative neoplasm unclassifiable. In the 2016 classification, mastocytosis is no longer considered a subgroup of the myeloproliferative neoplasms due to its unique clinical and pathologic features.

Myeloproliferative Neoplasm Treatment

In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera and intermediate- and high-risk primary myelofibrosis.

The FDA (2011) 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.[3] The Randomized Study of Ruxolitinib Tablets Compared to Best Available Therapy in Subjects With Primary Myelofibrosis, Post-Polycythemia Vera-Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis (COMFORT-II trial [2013]) compared ruxolitinib with best available therapy in individuals who had intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS.[4] 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.[5] In 2019, the FDA also approved fedratinib (InrebicUS) for adults with intermediate-2 or high-risk primary or secondary myelofibrosis based on results from a double-blind, randomized, placebo-controlled trial that found improvement in spleen volume and myelofibrosis-related symptoms.[6]

Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most individuals 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 reduced-intensity conditioning for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders. Allo-HCT is discussed in more detail in the next section.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer individuals who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. 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.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and individual is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the individual at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation 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 effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to individuals who are sufficiently fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which also increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This

permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced Intensity Conditioning for Allo Hematopoietic Cell Transplantation

Reduced-intensity conditioning refers to the pre-transplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of reduced-intensity conditioning is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of reduced-intensity conditioning is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Reduced-intensity conditioning regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo reduced-intensity conditioning with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. For the purposes of this policy, reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Summary of Evidence

For individuals who have myelodysplastic syndrome (MDS) who receive myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes systemic reviews, randomized controlled trials (RCTs), and numerous case series, which are often heterogeneous in terms of diseases included. The relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. 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 individual populations, conditioning regimens, and other factors. Reported estimates for 3 to 5-year OS of 40% to 50% are typical. Evidence from randomized and nonrandomized comparisons has suggested that RIC may be used as a risk-adapted strategy in

high-risk individuals who are older and with more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than MAC HCT. At present, HCT is the only potentially curative treatment option for individuals with MDS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have myeloproliferative neoplasms who receive MAC or RIC allo- HCT, the evidence includes a systematic review and retrospective observational series. The relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Evidence has suggested that RIC may be used as a risk-adapted strategy in high-risk individuals who are older and have more comorbidities without significantly worsening OS. 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 individuals with MDS and myeloproliferative neoplasms. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

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

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05367583	Cohort Study Assessing the Treatment Strategy for High-Risk Myelodysplastic Syndromes in Patients Under 70 (COMYRE)	107	Oct 2024
Unpublished			
NCT02757989	Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome Low Risk	79	June 2024

NCT: national clinical trial.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network clinical guidelines for myelodysplastic syndromes (v.1.2025) make the following general recommendation about allogeneic hematopoietic cell transplantation (allo-HCT)[53]:

> For individuals who are transplant candidates, an HLA [human leukocyte antigen]-matched sibling, or HLA-matched unrelated donor can be considered. 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 individuals. High-dose conditioning is typically used for younger individuals, whereas RIC [reduced-intensity conditioning] for HCT is generally the strategy in older individuals.

Specific National Comprehensive Cancer Network recommendations for HCT for treatment of myelodysplastic syndromes are outlined in **Table 4**.

Table 4: Guidelines for Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes

Prognostic Category	Recommendations for HCT
IPSS low/intermediate-1 **OR** IPSS-R very low, low, intermediate **OR** WPSS very low, low, intermediate	Consider allo-HCT for patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL, with poor probability

Prognostic Category	Recommendations for HCT
	of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy Consider allo-HCT for patients who have symptomatic anemia with del(5q), with inadequate response/intolerance to lenalidomide and/or erythropoetin stimulating agents, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy
IPSS intermediate-2, high **OR** IPSS-R intermediate, high, very high **OR** WPSS high, very high	Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available

allo: allogeneic; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; WPSS: WHO Classification-based Prognostic Scoring System.

Table 5 summarizes the National Comprehensive Cancer Network recommendations (v.2.2024) on the use of allo-HCT for the treatment of myeloproliferative neoplasms.[54] 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.

Table 5: Guidelines for Allogeneic Hematopoietic Cell Transplantation for Myeloproliferative Neoplasms

Prognostic Category	Recommendations for Allo-HCT
Lower-risk myelofibrosis MIPSS-70≤3 MIPSS-70+ Version 2.0 ≤3 DIPSS-Plus ≤1 DIPSS ≤2 MYSEC-PM <14	In symptomatic patients with disease progression despite treatment with ruxolitinib, peginterferon alfa-2a, or hydroxyurea (if cytoreduction would be symptomatically beneficial), pacritinib, or momelotinib, consider allo-HCT immediately or bridging therapy 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
Higher-risk myelofibrosis MIPSS-70 ≥4 MIPSS-70+ Version 2.0 ≥4 DIPSS-Plus >1	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 all patients

Prognostic Category	Recommendations for Allo-HCT
DIPSS >2 MYSEC-PM ≥14	
Disease progression to advanced stage/AML	Bridging therapy followed by allo-HCT; bridging therapy options include: hypomethylating agents ± JAK inhibitors or venetoclax, or intensive induction chemotherapy, followed by allo-HCT

allo: allogeneic; AML: acute myeloid leukemia; DIPSS: Dynamic International Prognostic Scoring System; HCT: hematopoietic cell transplantation; MIPSS: Mutation-Enhanced International Prognostic Scoring System; MYSEC-PM: Myelofibrosis Secondary to PV [polycythemia vera] and ET [essential thrombocythemia]-Prognostic Model; JAK: Janus kinase.

American Society of Transplantation and Cellular Therapy

In 2020, the American Society of Transplantation and Cellular Therapy (formerly The American Society for Blood and Marrow Transplantation) published updated guidelines on indications for HCT and immune effector cell therapy based on the recommendations of a multiple-stakeholder task force.[55] **Table 6** summarizes categorizations for allo-HCT in adults.

Table 6. Recommendations for the Use of Hematopoietic Cell Transplantation to Treat Myelodysplastic Syndromes, Myelofibrosis, and Myeloproliferative Neoplasms

Indication	Recommendation
Myelodysplastic Syndromes	
Low/intermediate-1 risk	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")
Intermediate-2/high risk	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
Myelofibrosis and Myeloproliferative Neoplasms	
Primary, low risk	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
Primary, intermediate/high risk	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")

Indication	Recommendation
Secondary	Standard of care ("well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies")
Hypereosinophilic syndromes, refractory	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")

HCT: hematopoietic cell transplantation

In 2022, the ASTCT published practice recommendations for HCT in the management of myelodysplastic syndromes. A standardized system for grading the levels of evidence was applied (as recommended by the ASTCT Steering Committee for evidence-based reviews). **Table 7** summarizes allo-HCT specific recommendations by ASTCT.

Table 7. Recommendations for the Use of Allogeneic Hematopoietic Cell Transplantation to Treat Myelodysplastic Syndromes

Indication/ Consideration	Recommendation	Grade of Recommendation
Should allogeneic HCT routinely be offered early for advanced (int-2/high) de novo MDS?	Yes	A
Should allogeneic HCT routinely be offered early for lower risk (low/int-1) de novo MDS?	No	B

HCT: hematopoietic cell transplantation; MDS: myelodysplastic syndrome.

Medicare National Coverage

There is a national coverage determination for stem cell transplantation (110.23; formerly 110.81),[56] portions of which are highlighted below:

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, DIPSS plus 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 US 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 title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

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History

Date	Comments
02/01/00	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.
11/12/02	Replace policy - Policy reviewed with no criteria changes.
07/13/04	Replace policy - Policy reviewed with literature; policy statement also now includes "mini-transplant." References added; cross-reference to BC.8.01.38 on mini-transplants added.
07/12/05	Replace policy - Policy reviewed with literature search; no change in policy statement. No further review scheduled.
02/06/06	Codes updated - No other changes.
06/02/06	Disclaimer and Scope Updates - No other changes.
10/09/07	Replace policy - Policy updated with literature review. Status changed from AR to BC. References added. No change in policy statement.
11/12/07	Codes updated - CPT code 86817 removed as directed by RPIW.
05/13/08	Cross Reference Update - No other changes

Date	Comments
03/10/09	Replace policy - Policy updated with literature search. Minor terminology changes to policy statements; the intent of the policy statements remain unchanged. Additional policy statements include Reduced intensity conditioning allogeneic SCT is considered investigational as a treatment of myeloproliferative disorders and myelodysplastic syndrome. References and codes added. "High-Dose Chemotherapy" removed from the title and throughout the body of the policy and "myeloproliferative" diseases added to the policy title.
12/08/09	Code Update - 86817 code added back to the policy.
02/09/10	Code Update - New 2010 codes added.
03/08/11	Replace policy - Policy updated with literature search, reference numbers 14-17 added. Myeloproliferative Disorders" replaced with "Myeloproliferative Neoplasms" in title and text. Policy statements revised to indicate that RIC HCT, previously investigational, may now be considered medically necessary as a treatment of myelodysplastic syndrome and myeloproliferative neoplasms in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Reviewed and recommended by OAP in February 2011.
10/19/11	Related Policies updated; links refreshed.
01/06/12	Replace policy – Policy updated with literature search; references 15-18 and 20 added. Policy statements unchanged. ICD-10 codes added.
01/24/12	Code 38232 added.
02/09/12	CPT code 38204 was removed from the policy.
06/20/12	Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.
08/01/12	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.
10/01/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
01/29/13	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.
09/30/13	Update Related Policies. Change title to 8.01.31.
10/18/13	Update Related Policies. Change title to 8.01.17.
01/21/14	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.
02/27/14	Update Related Policies. Change title to 8.01.30.
03/21/14	Update Related Policies. Add 8.01.15 and delete 8.01.514.

Date	Comments
04/18/14	Update Related Policies. Remove 8.01.20 and add 8.01.529.
06/24/14	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.
12/03/14	Update Related Policies. Remove 8.01.21 and 8.01.26.
01/28/15	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.
02/19/15	Update Related Policies. Remove 8.01.30.
05/01/16	Annual Review, approved April 12, 2016. Policy updated with literature review through October 27, 2015. References 1, 8, 21-22, 36-38, 43, and 48 added. Policy statements unchanged. Update effective May 1, 2016.
09/01/16	Update Related Policies. Remove 8.01.27 as it was archived.
09/30/16	Coding Update. Remove CPT 86817 from coding section.
11/04/16	Coding update. Removed codes that are transplant benefit related.
04/01/17	Annual Review, approved March 14, 2017. Policy name changed to Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms. Policy updated with literature review through November 7, 2016; references 37-38 and 49-50 added. Changed "hematopoietic stem cell transplantation" to "hematopoietic cell transplantation" per NCCN terminology change. Policy statements unchanged.
08/01/17	Updated title of Related Policy 8.01.511.
11/10/17	Policy moved to new format, no changes to policy statement.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references updated. Removed investigational policy statements.
09/01/18	Minor update. Re-added Consideration of Age information, which was in advertently removed during a previous update.
04/01/19	Annual Review, approved March 19, 2019. Policy updated with literature review through October 2018; no references added. Policy statements unchanged.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020 and replaced with InterQual criteria for dates of service on or after July 2, 2020.
05/01/20	Annual Review, approved April 14, 2020. Policy updated with literature review through November 2019; references added; new description of HCT added; Policy statement for RIC allo-HCT changed to specify it as a risk-adapted strategy for patients at high-risk of MAC intolerance, which is meant to encompass both older age and medical co-occurring conditions; RCT evidence review and updates to Policy Coverage Criteria section support the existing medically necessary policy statement for RIC allo-HCT and supplants the 2009 clinical input which has been removed.

Date	Comments
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.
04/01/21	Annual Review, approved March 2, 2021. Policy updated with literature review through November 16, 2020; no references added. Policy statements unchanged. Update Related Policies, removed reference to 8.01.22 and replaced with 8.01.538.
5/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
04/01/22	Annual Review, approved March 7, 2022. Policy updated with literature review through November 13, 2021; references added. Policy statements unchanged.
04/01/23	Annual Review, approval March 6, 2023. Policy updated with literature review through November 15, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Policy renumbered from 8.01.21 to 8.01.539 Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, approved March 12, 2024. Policy updated with literature review through November 13, 2023; reference added. Policy statements unchanged.
10/09/24	Minor update. Removed policy 8.01.538 Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias from the Related Policy section.
04/01/25	Annual Review, approved March 10, 2025. Policy updated with literature review through December 9, 2025; no references added. Policy statements unchanged.

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