

Subject: Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes (MDS)		Original Effective Date: 3/8/2018
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.¹

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL ^{34 36}

Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) consist of a heterogeneous group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production and a varying risk of transformation to acute leukemia. Patients with MDS have reductions in the production of red blood cells, platelets, and mature granulocytes and these abnormalities often result in anemia, bleeding, and increased risk of infection. MDS occur predominantly in older patients (usually those older than 60 years), with a median age at diagnosis of approximately 70 years, although patients as young as 2 years have been reported. Older men are more commonly affected by MDS (median age at diagnosis 65-70 years), but the isolated chromosome 5q deletion subtype (del5q) is more common in women. Signs and symptoms at presentation of MDS are nonspecific. Many patients are asymptomatic at diagnosis and only come to the physician's attention based upon abnormalities found on routine blood counts (eg, anemia, neutropenia, and thrombocytopenia). Others present with symptoms or complications resulting from a previously unrecognized cytopenia (eg, infection, fatigue). The diagnosis of MDS is made based upon an evaluation of the bone marrow and peripheral smear. The revised IPSS (IPSS-R) (calculator 1) should be used to incorporate information on bone marrow blast percentage, karyotype, and cytopenias for the purpose of stratifying the MDS into risk groups to guide management. Patients with a very low (≤ 1.5 points) or low (>1.5 to 3 points) IPSS-R score are primarily treated with supportive care or low intensity therapies such as azacitidine or decitabine or immunosuppressive therapy. Patients with a high (>4.5 to 6 points) or very high (>6 points) IPSS-R score with a good performance status are primarily treated with combination chemotherapy or allogeneic HCT in an attempt to alter the disease course. Treatment options for patients with an intermediate-risk (>3 to 4.5 points) IPSS-R score include those therapies used for patients with low- or very low-risk IPSS-R scores, and the more intensive therapies typically used for patients with high- or very high-risk IPSS-R scores. Allogeneic hematopoietic cell transplantation (HCT) is a treatment option for patients with intermediate, high, or very high-risk MDS.

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

Pretransplant Evaluation

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

RECOMMENDATION

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet UNOS guidelines for transplantation and the diagnosis must be made by a *Specialist in the Disease* and or Transplant Surgeon.

Pre-Transplant Evaluation: 2-10 34 35

Criteria for transplant evaluation include all of the following:

- History and physical examination
- Psychosocial evaluation and clearance:
 - No behavioral health disorder by history or psychosocial issues:
 - if history of behavioral health disorder, no severe psychosis or personality disorder
 - mood/anxiety disorder must be excluded or treated
 - member has understanding of surgical risk and post procedure compliance and follow-up required
 - Adequate family and social support
- EKG

- Chest x-ray
- Cardiac clearance in the presence of any of the following:
 - chronic smokers
 - > 50 years age
 - those with a clinical or family history of heart disease or diabetes
- Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- Neurological exam and clearance for transplant: [ONE]
 - Normal exam by H&P
 - Abnormal neurological exam with positive findings: [ONE]
 - Lumbar puncture normal cytology
 - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- Performance Status : [ONE]
 - Karnofsky score 70-100%; or
 - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- Lab studies:
 - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
 - *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
 - If HIV positive all of the following are met:
 - CD4 count >200 cells/mm-3 for >6 months
 - HIV-1 RNA undetectable
 - On stable anti-retroviral therapy >3 months
 - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
 - If abnormal serology need physician plan to address and/or treatment as indicated
 - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
- *GYN examination with Pap smear for women ≥21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant
- *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

**Participating Centers of Excellence may waive these criteria*

Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation: 2-10 34 35

1. *Hematopoietic Allogeneic stem-cell transplantation (HSCT) ablative or non-myeloablative* from a human leukocyte antigen (HLA)-matched donor (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and

HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized in adults and children for the treatment of Myelodysplastic Syndromes (MDS) when ANY of the following criteria are met:

- All pre-transplant criteria are met; and
- In patients with any of the following clinical indications:
 - Any intermediate or high IPSS or IPSS-R score* defined as having an IPSS-R score of >3-4.5 (intermediate) or >4.5 (high/very high); or
 - Any MDS with poor prognostic features including any of the following:
 - Treatment related MDS;
 - Refractory cytopenias;
 - Adverse cytogenetics and molecular features;
 - Transfusion dependence;
 - Failure of hypomethylating agents or chemotherapy;
 - Moderate to severe marrow fibrosis

**Note: Risk stratification is according to the International Prognostic Scoring System (IPSS).¹⁰ This score is available at: <http://www.mds-foundation.org/ipss-r-calculator/>*

AND

- The requesting transplant recipient should not have any of the following **absolute contraindications**:
 - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
 - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
 - Systemic and/or uncontrolled infection
 - AIDS (CD4 count < 200cells/mm³)
 - Unwilling or unable to follow post-transplant regimen
 - ◇ Documented history of non-compliance
 - ◇ Inability to follow through with medication adherence or office follow-up
 - Chronic illness with one year or less life expectancy
 - Limited, irreversible rehabilitation potential
 - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
 - No adequate social/family support
- The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
 - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
 - Smoking, documentation supporting free from smoking for 6 months
 - Active peptic ulcer disease
 - Active gastroesophageal reflux disease
 - CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
 - Obesity with body mass index of >30 kg/m² may increase surgical risk

- Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
- Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

2. A second or repeat *Hematopoietic Allogeneic stem cell transplantation* (ablative or non-myeloablative) may be authorized only one time for members with MDS who meet all of the above criteria for transplant and have any of the following: [ONE]

- primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; or
- failure to engraft*
- late relapse (greater than 18 months after HCT) as salvage therapy

**Note: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds $5 \times 10^9/L$ or $> ANC500$ at any time after transplantation.³*

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
 - Presence of no absolute contraindication as listed above;
 - History and physical within the last 12 months;
 - Kidney profile within the last 12 months;
 - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
 - Psychosocial evaluation or update within the last 12 months;
 - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.
- If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
 - Authorization letter/documentation from previous insurer;
 - Presence of no absolute contraindication as listed above;
 - History and physical within the last 12 months;
 - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
 - Psychosocial evaluation or update within the last 12 months;
 - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

COVERAGE EXCLUSIONS ^{2-10 34 35}

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. A second or repeat autologous or allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive or early relapsed disease.
3. Autologous stem cell transplantation
4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered

There have been no prospective trials evaluating the timing of allogeneic HCT in patients with MDS. Observational studies and clinical decision analyses suggest that patient's with intermediate, high, or very high risk IPSS-R scores and those with intermediate-2 or high risk IPSS scores are most likely to benefit from allogeneic HCT; patients with lower scores are better served by delaying transplantation until progression to higher risk disease, but before transformation to acute myeloid leukemia. ^{12 13} The risk of treatment related mortality (TRM) following transplantation varies according to both transplant-related factors (preparative regimen, donor source, HLA-disparity) and patient-related factors (age, comorbidities). TRM is expected to be highest for older patients with comorbidities who undergo a myeloablative transplant from a partially matched unrelated donor as described by Sierra et al. 387 patients with MDS who underwent myeloablative HLA-matched sibling HCT, TRM at one and three years were 32 and 37 percent, respectively and increased with age. When compared with younger patients, TRM was increased in patients 18 to 30 years (relative risk [RR] 2.9), 31 to 45 years (RR 4.1), and older than 45 years (RR 4.4). ³⁰

Saber et al. (2013) performed analysis of post-HCT outcomes for MDS. Outcomes of 701 adult MDS patients who underwent HCT between 2002 and 2006 were analyzed: (MRD [n = 176], 8 of 8 HLA-A, -B, -C, -DRB1 allele matched MUD [n = 413], 7 of 8 MUD [n = 112]). Median age was 53 years (range of 22 to 78 years). In multi-variate analyses, MRD HCT recipients had similar DFS and survival rates compared with 8 of 8 MUD HCT recipients (relative risk [RR] 1.13 respectively), and both MRD and 8 of 8 MUD had superior DFS (RR 1.47 respectively) and survival (RR 1.62 and 1.30 respectively) compared with 7 of 8 MUD HCT recipients. The authors concluded that in patients with MDS, MRD remains the best stem cell source followed by 8 of 8 MUD; transplantation from 7 of 8 MUD is associated with significantly poorer outcomes. ²⁶

Komrokji et al. (2016) indicated that the higher risk MDS patients, defined by the IPSS as intermediate-2 or high-risk groups, consist of 1/3 of MDS patients who have an expected survival of less than 1.5 years. The ability to better define higher risk MDS improved with the proposal of new clinical risk models such as the revised IPSS and by integration of molecular data, including somatic gene mutations; AHSCT remains the only curative option. In higher risk MDS patients, proceeding early with AHSCT is associated with maximum survival gain. The decision to pursue AHSCT is individualized according to disease risk, co-morbidities, and functional status. The role of therapy before AHSCT remains controversial, and the role of post-AHSCT maintenance is evolving. Hypomethylating agents are the only medications that change the natural history of the disease. Azacitidine is the only drug reported to improve OS in higher risk MDS patients. Appropriate use and assessment of response is key for assuring patients benefit of such limited options. Treatment after failure of hypomethylating agents is an unmet need. The role of detectable somatic gene mutations in prognosis and tailoring therapy continue to emerge. ²²

In summary, the published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of MDS in selected individuals. However, improved outcomes have not been demonstrated for autologous HSCT compared with conventional chemotherapy in individuals with MDS therefore the role of autologous HSCT for this indication has not been established.

Professional Organizations ²⁻¹⁰

The American Society for Blood and Marrow Transplantation (2009) clinical guideline on The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes stated that a HLA-matched allogeneic donor (sibling, other family member, unrelated individual, or cord blood) SCT is recommended if an appropriate donor is available and that there are sufficient data demonstrating a long term curative outcome for related and unrelated allogeneic SCT. ²

National Comprehensive Cancer Network (NCCN): The NCCN Guidelines (2018) for Myelodysplastic Syndromes recommend that allogeneic HSCT from an HLA-matched sibling donor or matched unrelated donor is a preferred approach for treating a selected group of patients with MDS, particularly those with high-risk disease. This includes both standard and RIC strategies. In patients who relapse after a prolonged remission following the first transplant, a second transplant or donor lymphocyte infusion immune based therapy may be considered. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been established. Comparative clinical trials are needed to address these issues.⁹

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
Collection Codes	
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
Cell Processing Services	
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
Cell infusion codes	
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

ICD-10	Description: [For dates of service on or after 10/01/2015]

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