

Molina Clinical Policy

Hematopoietic Stem Cell Transplantation for Multiple Myeloma and POEMS Syndrome: Policy No. 122

Last Approval: 6/14/2023

Next Review Due By: June 2024



DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. 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 (e.g., 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 MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Multiple myeloma is a rare form of cancer identified by excessive production (proliferation) and improper function of certain cells (plasma cells) found in the bone marrow. Plasma cells (white blood cells) produced in the bone marrow normally reside there however, excessive cells may eventually mass together to form a tumor or tumors in the body, specifically the bone marrow. Solitary plasmacytoma refers to cases where only a single tumor is present; multiple myeloma refers to cases with multiple tumors present or the bone marrow has greater than 10% plasma cells. Plasma cells play a crucial role in the immune system and secrete a type of antibody called immunoglobulin proteins (M-proteins). An overproduction of plasma cells leads to unusually high levels of M proteins (NORD 2023). The main symptoms of multiple myeloma may include bone pain (especially in the back and ribs); anemia leading to weakness, fatigue, and lack of pallor; and renal abnormalities. Pneumonia may also be present in those prone to bacterial infections (NORD 2023).

While rare, approximately 100,000 Americans currently have multiple myeloma, and it accounts for 10% of all hematological malignancies diagnoses in the United States. Diagnoses are slightly higher in males than females and is typically discovered between the fourth and seventh decade of life (average age at diagnosis is 68) (NORD 2023). In 2022, an estimated 34,470 new cases of multiple myeloma are expected to be diagnosed which accounts for 1.8% of all new cancer cases. An estimated 12,640 deaths are expected in 2022, accounting for 2.1% of all cancer deaths. (NIH 2022).

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)

Patients who have been newly diagnosed are evaluated to verify the diagnosis as the premalignant stages of multiple myeloma. MGUS and SMM can be misdiagnosed as multiple myeloma. For example, patients with MGUS can have renal failure as a result of diabetes or hypertension or have bone lesions from other types of cancers. These patients may be misdiagnosed with multiple myeloma if findings are incorrectly attributed to the plasma cell dyscrasia. In patients that have end-organ damage, it should be determined if it is truly secondary to the underlying plasma cell disorder or to an unrelated process. (Laubach 2023).

MGUS is characterized by the presence of M-proteins in the blood; levels found in the urine may be low. Patients who do not have the physical symptoms associated with multiple myeloma (e.g., anemia, bony lesions, kidney abnormalities). Some patients ultimately develop a malignant disorder such as multiple myeloma, Waldenstrom macroglobulinemia, or amyloidosis (NORD 2023).

Patients with SMM have more myeloma cells than someone with asymptomatic myeloma or MGUS. At this stage, the disease may cause bone damage, anemia, kidney problems, or hypercalcemia. Levels of M protein and plasma cells in the bone marrow are higher in patients with SMM than those with MGUS (10-60% of all cells in marrow are plasma cells). However, there is still no evidence of symptoms or signs of myeloma, such as significant bone disease or anemia. Bisphosphonates may be prescribed for patients with symptoms of osteoporosis or osteopenia. Most people with SMM eventually develop myeloma. Patients should be monitored – treatment may be recommended if the disease progresses, specifically in patients at risk of developing symptoms within 18 months to 2 years. (ASCO 2021).

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Those with a confirmed diagnosis of multiple myeloma require treatment whereas those with MGUS and SMM do not; symptomatic patients die within a median of six months without effective therapy. Patients with SMM may remain stable for prolonged length of time. In patients with SMM and multiple myeloma, it is reasonable to re-evaluate the patient in two or three months and to delay therapy until the correct diagnosis is evident. Symptoms should be monitored by the patient and the Provider should be notified immediately if there are changes. (Laubach 2023).

Staging

There are three staging systems used for multiple myeloma – the Durie-Salmon Staging System, the International Staging System (ISS) and the Revised International Staging System (R-ISS):

Stage	Durie-Salmon Staging Criteria (¹ IMF 2021)	International Staging System (ISS) Criteria (² IMF 2021)	Revised International Staging System (R-ISS) Criteria (ASCO 2021, ² IMF 2021)
I	All of the following: <ul style="list-style-type: none"> Hb > 10g/dL Normal serum calcium or <10.5mg/dL Skeletal survey – normal or single plasmacytoma or osteoporosis Low M component production rate: <ul style="list-style-type: none"> Serum paraprotein level IgG < 5 g/dL Serum paraprotein level IgA < 3 g/dL Urinary light chain M-component on electrophoresis < 4 g/24h 	Serum beta-2 microglobulin < 3.5mg/L Serum Albumin ≥ 3.5g/dL	All of the following: <ul style="list-style-type: none"> Serum beta-2 microglobulin < 3.5mg/L Serum Albumin ≥ 3.5g/dL Normal LDH No high-risk chromosome changes in myeloma cells found by fluorescence in-situ hybridization (FISH) test
II	Neither Stage I or III	Neither stage I or III	Neither stage I or III
III	One or more of the following: <ul style="list-style-type: none"> Hb < 8.5g/dL High calcium > 12 mg/dL Advanced lytic bone lesions (scale 3) High M component production rate: <ul style="list-style-type: none"> Serum paraprotein level IgG > 7g/dL Serum paraprotein level if IgA, > 5 g/dL Urinary light chain M-component > 12 g/24h 	Serum beta-2 microglobulin < 5.5mg/L	Serum beta-2 microglobulin > 5.5mg/L, plus one of the following: <ul style="list-style-type: none"> Myeloma cells have high-risk chromosome changes found by FISH test High LDH
Notes	Sub-classification criteria: A: Normal renal function: serum creatinine < 2 mg/dL B: Abnormal renal function: serum creatinine > 2 mg/dL		

The R-ISS was developed in 2015 by the International Myeloma Working Group to account for the FISH test and LDH levels (IMF 2021). According to ASCO (2021), “the R-ISS is most commonly used to predict prognosis [and] higher blood levels of LDH indicate a poorer prognosis.”

Hematopoietic Stem Cell Transplant (HSCT)

Once risk stratification has been completed, patients are assessed to determine eligibility for autologous HSCT. Compared with chemotherapy alone, autologous HSCT appears to prolong both event-free and overall survival. Stem cell collection should occur early during treatment, independent of if the plan is for HSCT to be incorporated into the initial treatment or postponed until the time of first relapse. Eligibility for autologous HSCT in patients with multiple myeloma varies across countries and institutions. The United States does not have a strict age limit and decisions are made on a case-by-case basis. Most centers consider patients ineligible for autologous HSCT if any of the following criteria are present:

- Over age 77
- Frank cirrhosis of the liver
- Eastern Cooperative Oncology Group (ECOG) performance status 3 or 4 unless due to bone pain
- New York Heart Association functional status Class III or IV

Autologous HSCT involves the use of a patient’s own hematopoietic cells to reconstitute the bone marrow following

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treatment for cancer with intensive chemotherapy and/or radiation therapy. This contrasts with allogeneic HSCT, in which hematopoiesis is restored using hematopoietic cells from another individual (e.g., a sibling, volunteer donor, other relative, or umbilical cord blood). Autologous HSCT is indicated for multiple myeloma. It is also indicated for Hodgkin lymphoma, diffuse large B cell lymphoma, follicular lymphoma, peripheral T cell lymphoma, mantle cell lymphoma, acute myeloid leukemia, amyloidosis, Waldenström macroglobulinemia, and testicular germ cell cancer. A registry study found that when compared with younger patients, over 2000 patients age ≥ 70 experienced similar outcomes following autologous HSCT for multiple myeloma. (Holmberg et al. 2022).

Autologous

Current recommendations for treatment of multiple myeloma in patients newly diagnosed and under age 70 includes high-dose therapy followed by autologous HSCT. It should be performed at the time of initial diagnosis or at relapse. While not curative, this combined treatment may improve chances of event-free survival and overall survival compared to standard-dose myeloma treatments alone. Candidates for autologous HSCT undergo induction chemotherapy – it is administered for approximately four months prior to stem cell collection in an effort to reduce the number of tumor cells in the patient’s bone marrow and peripheral blood as well as improve symptom outcomes and alleviate end-organ damage. An induction regimen may include bortezomib, lenalidomide, dexamethasone (VRd). (Kumar 2023).

Many patients are prescribed a preparative regimen of high-dose melphalan (200 mg/m²) rather than lower-dose melphalan plus total body irradiation or more intensive preparative regimens. (Patients with serum creatinine >2.0 mg/dL at the time of transplantation may receive a lower dose of melphalan, typically 140 mg/m²). Patients over age 65 and who are candidates for HSCT, a single dose of melphalan (200 mg/m²) is recommended as the conditioning regimen versus tandem intermediate-dose melphalan 100 mg/m². Patients over age 70 are recommended to receive a lower dose of melphalan (140 mg/m²). (Kumar 2023).

Treatment for patients with relapsed multiple myeloma following an autologous HSCT include: a second autologous HSCT, allogeneic HSCT as part of a clinical trial, or treatment with salvage chemotherapy regimens. A second autologous HSCT is a reasonable approach for patients who are transplant-eligible and have attained a response duration longer than 18 months (without maintenance therapy) or more than 36 months (with maintenance therapy). Patients under age 65 and who have a suitable matched donor, non-myeloablative allogeneic HSCT or salvage chemotherapy is a potential treatment. (Kumar 2023).

Allogenic

A minority of patients will be eligible for allogeneic HSCT, but the role of allogeneic approaches in multiple myeloma remains investigational and controversial (Laubach 2023). Allogeneic HSCT has the potential for producing cure in patients with multiple myeloma. Use is limited however, as even ideal candidates have a high rate of treatment-related mortality. In addition, efficacy of allogeneic HSCT compared to autologous HSCT has not been fully studied. Mortality related to allogeneic HSCT is decreasing due to the advent of nonmyeloablative preparative regimens. New chemotherapeutic agents (e.g., bortezomib, lenalidomide) are also being combined with initial treatment of multiple myeloma; survival is increasing with chemotherapy alone or with autologous HSCT. The use of allogeneic HSCT requires additional study for the treatment of multiple myeloma. (Kumar 2023).

POEMS Syndrome

POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is distinguished by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of the following (Dispenzieri 2023):

- Osteosclerotic myeloma *
- Castleman disease (angiofollicular lymph node hyperplasia) *
- Increased levels of serum vascular endothelial growth factor (VEGF) *
- Organomegaly
- Endocrinopathy
- Edema
- Typical skin changes

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- Papilledema
- * Major criteria for diagnosis of POEMS Syndrome

MGUS results when monoclonal protein, an abnormal protein, is detected in the blood. While MGUS typically is not problematic, symptoms can include numbness, tingling or weakness. For some patients, MGUS eventually progresses into other types of blood cancer (e.g., multiple myeloma, macroglobulinemia or B-cell lymphoma). Osteosclerotic myeloma is also a form of multiple myeloma. When symptoms other than CRAB (hypercalcemia, renal dysfunction, anemia, or sclerotic bone lesions), consideration of a POEMS syndrome diagnosis should be explored. Patients typically have symptoms similar to classic multiple myeloma however, instead of the patient having thin and holey bones, osteosclerosis is found (a condition evidenced by abnormal density and hardening of bone) (NORD 2021).

COVERAGE POLICY

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 reviewed 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.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Transplant Evaluation

(AMR 2019; CMS 2016; Holmberg 2022; ECOG date unknown; ¹⁻⁴NMDP date unknown)

Please see MCP-323 Pre-Transplant Evaluation for additional criteria and information.

Criteria for transplant evaluation include:

1. History and physical examination; **AND**
2. Psychosocial evaluation and clearance:
 - a. 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.
 - AND**
 - b. Adequate family and social support.

AND

3. EKG; **AND**
4. Chest x-ray; **AND**
5. Cardiac clearance in the presence of any of the following:
 - a. Chronic smokers; **OR**
 - b. Members > 50 years age; **OR**
 - c. Those with a clinical or family history of heart disease or diabetes.

AND

6. Pulmonary clearance if evidence of pulmonary artery hypertension or chronic pulmonary disease; **AND**

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7. Neurological exam and clearance for transplant including **ONE** of the following:
- Normal neurologic exam; **OR**
 - Non-life limiting neurological impairment that does not preclude transplant and not caused by hematologic malignancy (e.g., diabetic peripheral neuropathy); **OR**
 - Abnormal neurological exam with positive findings including **ONE** of the following:
 - Lumbar puncture normal cytology; **OR**
 - Lumbar puncture with cytological exam abnormal, however central nervous system disease treated prior to clearance.

AND

8. A Performance Status that includes **ONE** of the following:
- Karnofsky score 70-100%; **OR**
 - Eastern Cooperative Oncology Group (ECOG) Grade 0-2.

AND

9. Lab studies that include:
- Complete blood count; kidney profile (blood urea nitrogen, creatinine); electrolytes; calcium; phosphorous; albumin; liver function tests; and coagulation profile (prothrombin time, and partial thromboplastin time);*
 - Serologic screening for: Human Immunodeficiency (HIV); Epstein Barr virus (EBV); Hepatitis B virus (HBV); Hepatitis C virus (HCV); cytomegalovirus (CMV); rapid plasma reagin (RPR) and/or fluorescent treponemal antibody (FTA):*
 - If HIV positive **ALL** of the following must be met:
 - CD4 count >200 cells/mm³ for >6 months; **AND**
 - Human Immunodeficiency Virus 1 (HIV-1) ribonucleic acid undetectable; **AND**
 - On stable anti-retroviral therapy >3 months; **AND**
 - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm).
 - Urine drug screen if Member is current or gives a history of past drug abuse.

AND

10. Colonoscopy (if indicated or if Member is age \geq 45) with complete workup and treatment of abnormal results as indicated; an initial screening colonoscopy after initial negative screening requires a follow-up colonoscopy every 10 years).*

AND

11. Gynecological examination with Pap smear for women ages \geq 21 to \leq 65 years of age or if indicated (not indicated in women who have had a total abdominal hysterectomy or a total vaginal hysterectomy) within the last three years 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; **AND**
- Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated;* **AND**
- Prostate Specific Antigen (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 HSCT

- Autologous HSCT may be considered medically necessary to

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treat multiple myeloma or POEMS syndrome for Members with **ONE** of the following:

- a. Diagnosis of Durie-Salmon Stage II or III multiple myeloma and **ONE** of the following:
 - A partial response to post induction therapy defined as a 50% decrease either in measurable paraprotein (serum and/or urine) or in bone marrow infiltration sustained for at least 1 month; **OR**
 - Relapsed disease post induction therapy defined as increased M proteins in serum and urine; **OR**
 - Refractory disease post induction chemotherapy defined as disease that is unresponsive to post induction chemotherapy.
- OR**
- b. Diagnosis of disseminated POEMS syndrome defined as diffuse sclerotic lesions or disseminated bone marrow involvement
2. A second autologous HSCT may be considered medically necessary for the treatment of responsive multiple myeloma or POEMS syndrome that has relapsed after a durable complete or partial remission following an autologous HSCT.
 3. Allogenic HSCT may be considered medically necessary to treat multiple myeloma for individuals with early relapse (less than 24 months) after primary therapy that included an autologous HSCT.
 4. Tandem HSCT may be considered medically necessary for individuals with active multiple myeloma and the first and second transplantation should be within a 6-month period for either of the following:
 - Autologous-autologous tandem HSCT; **OR**
 - Initial autologous HSCT followed by reduced-intensity conditioning allogeneic HSCT.

In addition, the following must be met:

1. The requesting transplant recipient should not have any of the following **absolute contraindications**:
 - a. Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery; **OR**
 - b. Malignant neoplasm with a high risk for recurrence, non-curable malignancy (excluding localized skin cancer); **OR**
 - c. Systemic and/or uncontrolled infection; **OR**
 - d. AIDS (CD4 count < 200cells/mm³); **OR**
 - e. Unwilling or unable to follow post-transplant regimen as evidenced by **ONE** of the following:
 - Documented history of non-compliance; **OR**
 - Inability to follow through with medication adherence or office follow-up.
- OR**
- f. Chronic illness with one year or less life expectancy; **OR**
 - g. Limited, irreversible rehabilitation potential; **OR**
 - h. Active untreated substance abuse issues (requires documentation supporting that Member is free from addiction for minimally 6 months if previous addiction was present); **OR**
 - i. No adequate social or family support.

AND

2. The requesting transplant recipient should be evaluated carefully and potentially treated if any of the relative contraindications below are present. (Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation).
 - a. Smoking, documentation supporting free from smoking for 6 months; **OR**
 - b. Active peptic ulcer disease; **OR**
 - c. Active gastroesophageal reflux disease; **OR**
 - d. Cerebrovascular accident (CVA) with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months; **OR**
 - e. Obesity with body mass index of >30 kg/m² may increase surgical risk; **OR**
 - f. 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; **OR**

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- g. Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation.

Continuation of Therapy

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

1. If Molina Healthcare has authorized prior requests for transplantation **ALL** of the following information is required for medical review:
 - a. Presence of no absolute contraindication as listed above; **AND**
 - b. History and physical within the last 12 months; **AND**
 - c. Kidney profile within the last 12 months; **AND**
 - d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
 - e. Psychosocial evaluation or update within the last 12 months; **AND**
 - f. 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.
2. If authorized prior requests for transplantation were obtained from another insurer, **ALL** of the following information is required for medical review:
 - a. Authorization letter/documentation from previous insurer; **AND**
 - b. Presence of no absolute contraindication as listed above; **AND**
 - c. History and physical within the last 12 months; **AND**
 - d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
 - e. Psychosocial evaluation or update within the last 12 months; **AND**
 - f. 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.

For Members with Significant or Daily Cannabis Use

1. Documentation of compliance with a physician prescribed and managed program of abstinence, and a reasonable expectation that the Member will be abstinent from cannabis use during the transplant and immediate post-transplant time period. Daily cannabis use is an absolute contraindication for both transplant and pre-transplant evaluation unless there is a state mandate applicable for medical cannabis use and transplants, and there is documentation of Member compliance with a physician prescribed plan of care for prescribed cannabis use.
2. If the Member's cannabis use follows a formal, State-based program for managed medical cannabis, the request should include:
 - Documentation of the Plan of Care for medical cannabis (including the medical decision making that supports the use of medical cannabis); **AND**
 - Transplant Provider agreement with the Plan of Care (including agreement to be accountable for managing the Member's use of medical cannabis).

Limitations and Exclusions

1. Autologous (ablative or non-myeloablative) HSCT when the above criteria are not met.
2. HSC collection, storage, and freezing for a future unplanned transplant.
3. Allogeneic HSCT to treat POEMS syndrome.
4. Tandem HSCT for POEMS syndrome.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

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SUMMARY OF MEDICAL EVIDENCE

Costa et al. (2021) completed a meta-analysis comparing the long-term survival of patients with multiple myeloma receiving tandem autologous HSCT versus autologous-allogeneic HSCT. Included trials were prospective in nature, only included newly diagnosed patients, and the “conditioning regimen for the allogeneic transplant had to meet the Center for International Blood and Marrow Transplant research criteria for reduced intensity.” The analysis included 5 trials with a total of 1338 patients. A total of 899 patients were included in the tandem autologous group and 439 patients were included in the autologous-allogeneic group. The primary outcomes of the meta-analysis included overall survival (OS) and progression-free survival (PFS). Secondary outcomes were non-relapse mortality (NRM), cumulative incidence of relapse or progression, and post-relapse survival. The median follow-up period for all trials was 118.5 months. Overall results showed a lower risk of NRM in the tandem autologous HSCT group (6.9% at 5 years and 8.3% at 10 years) compared to the autologous-allogeneic group (17.4% at 5 years and 19.7% at 10 years). However, the risk of relapse or progression was higher in the tandem autologous group (69.7% at 5 years and 77.2% at 10 years) than the autologous-allogeneic group (52.4% at 5 years and 61.6% at 10 years). PFS rates at 5 years were 23.4% and 14.4% for 10 years in the tandem autologous group versus 30.1% at 5 years and 18.7% for the autologous-allogeneic group, indicating that patients in the autologous-allogeneic group had improved PFS. OS for the tandem autologous group at 5 years was 59.8% and 36.4% at 10 years compared to 62.3% at 5 years and 44.1% at 10 years for the autologous-allogeneic group, indicating that patients in the autologous-allogeneic group had improved OS. Post-relapse survival was improved in the autologous-allogeneic group with survival rates of 51.1% at 5 years compared to 37.0% for the tandem autologous group.

Khorochkov et al. (2021) completed a systematic review with the goal of determining circumstances that an allogeneic HSCT approach is either feasible, preferred, and/or cautionary in patients with multiple myeloma. The review included 16 moderate- to high-quality observational and randomized controlled trials. Overall findings suggest that autologous HSCT combined with high-dose pharmacotherapy is the first-line treatment for newly diagnosed patients that are transplant eligible. Findings also suggest that allogeneic HSCT may benefit high-risk patients, particularly those with a resistance to therapeutics. One study by Bryant et al. included in the review sought to observe the effects of pre-treatment variables on the success of allogeneic HSCT. The most important adverse variable found in that study was that a pre-salvage stage II or III on the International Staging System being associated with relapse and poorer survival. Combined autologous and allogeneic HSCT was shown “to enhance survival but not necessarily outcomes” and was also associated with fewer occurrences of relapse when compared to single or tandem autologous HSCT. However, the success of combined autologous and allogeneic HSCT was based on a small sample size, indicating studies with larger sample sizes are needed to confirm these results. Findings also suggest that patients who responded to pre-salvage therapy saw a benefit to progression-free and overall survival when radioimmunotherapy combined with reduced-intensity conditioning was used before allogeneic HSCT. Patients older than 55 years of age were typically associated with worse outcomes due to graft-versus-host disease. It is suggested that the care team evaluate pre-transplant factors including high-risk cytogenetics, age, and pre-salvage therapy International Staging System criteria before creating a treatment approach tailored to each individual patient.

Dhakal et al. (2018) completed a systematic review, conventional meta-analysis, and network meta-analysis to evaluate the role of high-dose therapy with melphalan followed by an autologous HSCT (HDT/ASCT) compared to standard-dose therapy (SDT) using novel agents. Tandem high-dose therapy and autologous HSCT (HDT2) was also compared to HDT/ASCT and SDT if reported. Inclusion criteria was phase 3 randomized controlled trials (RCTs) with a minimum follow-up period of 2 years and the RCT had to report PFS and/or OS. RCTs with small sample sizes (<100 patients) were excluded from the analysis. The meta-analysis included 4 RCTs with a total of 2421 patients and the network meta-analysis included 5 RCTs with a total of 3171 patients. The primary outcome observed for analysis was PFS and secondary outcomes included OS, complete response (CR), and treatment-related mortality (TRM). PFS was reported by all 4 studies included in the conventional meta-analysis. There was a combined odds ratio (OR) of 0.55 strongly in favor of HDT/ASCT. PFS was reported in all 5 studies in the network meta-analysis and showed that treatments based on HDT/ASCT were associated with a superior PFS compared to SDT and HDT2 had the most favorable outcomes compared to SDT. CR was reported in all 4 studies and showed an OR of 1.27 in favor of HDT/ASCT. OS was reported in 3 studies in the conventional meta-analysis and had a combined OR of 0.76 in favor of HDT/ASCT. Network meta-analysis of OS showed no significant impact on survival for either HDT/ASCT or HDT2 when compared to SDT. TRM was reported in 2 studies in the conventional meta-analysis and was very minimal (<1%)

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for both HDT/ASCT and HDT2 which was comparable to SDT. Meta-regression of PFS and OS showed a larger beneficial effect with a longer follow-up combined with HDT2.

National and Specialty Organizations

Several professional society organizations have recommended that autologous HSCT is the preferred method of treatment following primary therapy for eligible patients and is an option for primary progressive or refractory disease post induction treatment (NCCN 2022; NCI 2023; ¹⁻³NMDP date unknown).

The **National Comprehensive Cancer Network Guidelines (NCCN) (2022)** published guidelines for multiple myeloma and made the following recommendations:

- Autologous HSCT for active (symptomatic) myeloma proceeding after induction therapy to high-dose therapy and stem cell transplant.
- Additional treatment post-autologous HSCT may include a second autologous HSCT on or off clinical trial depending on the interval between the preceding stem cell transplant and documented progression.
- Tandem HSCT is recommended for active (symptomatic) myeloma for response or stable disease.
- Allogeneic HSCT is recommended for active (symptomatic) myeloma and may include nonmyeloablative (mini) following autologous HSCT or fully myeloablative, preferably in a clinical trial. Current data do not support mini-allografting alone. The same recommendation is applied to post-autologous HSCT scenarios for progressive disease and response or stable disease.
- For patients treated with or without a prior transplant, allogeneic HSCT is also a recommended option for transplant candidates with relapse or progressive disease.

The **Society for Immunotherapy of Cancer (SITC)** published a *Consensus Statement on Immunotherapy for the Treatment of Multiple Myeloma* (Shah et al. 2020).

The **International Myeloma Working Group (IMWG)** published the following documents (Moreau et al. 2021; Terpos et al. 2021):

- *Consensus Statement and Guidelines Regarding the Current Status of Stem Cell Collection and High-Dose Therapy for Multiple Myeloma and the Role of Plerixafor (AMD 3100)*
- *Group Consensus Approach to the Treatment of Multiple Myeloma Patients Who are Candidates for Autologous Stem Cell Transplantation*
- *Recommendations for the Treatment of Multiple Myeloma-Related Bone Disease*
- *Recommendations for the Treatment of Relapsed and Refractory Multiple Myeloma*

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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

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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	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS (Healthcare Common Procedure Coding System) Codes

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 posttransplant care in the global definition

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

6/14/2023	Policy reviewed, "Pre-Transplant Evaluation" changed to "Transplant Evaluation," new criteria 7b, clarification edit to criteria #8 that only one of the sub-criteria need to be met, removed abnormal serology statement under criteria 9b, criteria 10 changed to age 45 years, added an asterisk to criteria 11 to denote it may be waived by a participating Center of Excellence. Grammatical edits to Disclaimer section and "Documentation Requirements" under Coverage Policy section. Replaced "marijuana" with "cannabis." Supplemental Information section removed. Overview, Summary of Medical Evidence, and References sections updated. Added codes 38221, 38222, 86812, 86813, 86816, 86817 and code descriptions updated for other codes. ICD-10 codes.
6/8/2022	Policy reviewed, no changes to criteria; included section on marijuana use; updated Overview, Summary of Medical Evidence and Reference sections.
6/17/2020, 6/9/2021 6/19/2019	Policy reviewed, no changes to criteria, updated guidelines and references. Added criteria for POEMS Syndrome. For MM removed age limitation, revised the criteria for first, second and tandem stem cell transplant based on updated professional society guidelines, updated references. General recommendation and summary of medical evidence sections were condensed for ease of application.
9/13/2018 12/14/2016, 6/22/2017 8/12/2015	Policy reviewed, no criteria changes, reference section updated. Policy reviewed, no changes. Policy reviewed and updated with revisions made to the pre-transplant criteria, minor revision to the criteria to include upper age limit of 78, and criteria for Allogenic Stem Cell Transplantation was added. Guideline and reference sections were updated.
12/12/2012	New policy.

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