Medical Policy

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Title: BMT - Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma, Plasma Cell Leukemia, Plasmacytoma, and POEMS Syndrome

Description/Background

Multiple Myeloma
Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 18% of all hematologic cancers in the United States. Plasma cell leukemia (PCL) is a rare, yet aggressive form of multiple myeloma (MM) characterized by plasma cells circulating in the peripheral blood that can be detected on conventional peripheral blood smear examination. PCL can either originate de novo (primary PCL) or as a secondary leukemic transformation of MM (secondary PCL). POEMS syndrome, characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes, is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia. Plasma cell dyscrasias are treatable but rarely curable. Plasma cell neoplasms (plasma cell dyscrasias) are a group of entities characterized by the neoplastic proliferation of a single clone of plasma cells, typically producing a monoclonal immunoglobulin. Plasma cell neoplasms can present as a single lesion (solitary plasmacytoma) or as multiple lesions (multiple myeloma). Solitary plasmacytomas most frequently occur in bone (plasmacytoma of bone), but can also be found outside bone in soft tissues (extramedullary plasmacytoma).(68)

At diagnosis, most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of disease complications.(1-3)

The disease is staged by estimating tumor mass, based on various clinical parameters such as hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure. MM usually evolves from an asymptomatic premalignant stage (termed *monoclonal gammopathy of undetermined significance*). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are

observed because there is little evidence that early treatment of asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage.(1,2) In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized and referred to as smoldering MM. The overall risk of disease progression from smoldering to symptomatic MM is 10% per year for the first 5 years, approximately 3% per year for the next five years, and 1% for the next ten years.(1,2)

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) SYNDROME

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takatsuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia.(4,5) This complex, multi-organ disease was first described in 1938, but the acronym POEMS was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.(6) No single test establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence has suggested it is mediated by an imbalance of pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor α; vascular endothelial growth factor may also be involved.(5,7) However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in Table 1.(8) Both mandatory major criteria, at least 1 of the other major criteria, and at least 1 of the minor criteria are necessary for diagnosis.

Table 1. Criteria and Associations for POEMS Syndrome

Mandatory Major Criteria	Other Minor Criteria	Minor Criteria	Known Associations
Polyneuropathy	Castleman disease	Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)	Pulmonary hypertension/restrictive lung disease
Monoclonal plasma-proliferative disorder	Sclerotic bone lesions	Extravascular volume overload(edema, pleural effusion, ascites)	Clubbing
	Vascular endothelial growth factor elevation	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)	Thrombotic diatheses
		Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)	Weight loss
		Papilledema	Low vitamin B 12 levels
		Thrombocytosis/polycythemia	Diarrhea
		Hyperhidrosis	Hyperhidrosis

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.(9) Other large series have been described in the United States, France, China, and in India.(8) In general, patients with POEMS have a superior overall survival (OS) compared with that of MM (nearly 14 years in a large series).(7) However, given the rarity of POEMS, there is a paucity of RCT evidence for POEMS therapies.(8) Numerous approaches have been tried, including ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylating agents, tamoxifen, trans retinoic acid, and high-dose chemotherapy with autologous HCT support. Optimal treatment involves eliminating the plasma cell clone (e.g., by surgical excision or local radiotherapy for an isolated

plasmacytoma) or systemic chemotherapy in patients with disseminated disease (e.g., medullary disease or multiple plasmacytomas). Given the underlying plasma cell dyscrasia of POEMS syndrome, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, have also been investigated.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic cells are intravenously infused to restore bone marrow function in cancer patients 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 (allogeneic HCT [allo-HCT]). They can be newly harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (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 patient 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 destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pre-transplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient 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 bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allo-HCT
Reduced-intensity conditioning (RIC) 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 RIC 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 RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. RIC regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

MULTIPLE MYELOMA TREATMENT OVERVIEW
In the pre-chemotherapy era, the median survival for a patient diagnosed with MM was approximately seven months. After the introduction of chemotherapy (e.g., the alkylating agent melphalan in the 1960s), prognosis improved, with a median survival of 24 to 30 months and a 10-year survival of 3%. In a large group of patients with newly diagnosed MM, there was no difference in overall survival reported during a 24-year period from 1971-1994, with a trend toward improvement during 1995-2000, and a statistically significant benefit in overall survival during 2001-2006.(2) These data suggested that autologous HCT was responsible for the trends during 1994-2000, while novel agents have contributed to the improvement since 2001.

The introduction of novel agents and better prognostic indicators has been the major advances in the treatment of this disease.(10,11) Novel agents such as the proteasome inhibitors (e.g., bortezomib), the monoclonal antibody daratumumab, and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed and refractory myeloma and now have been integrated into first-line regimens.(10-13) With the introduction of these novel treatments, it is now expected that most patients with MM will respond to initial therapy, and only a small minority will have refractory disease.(14)

Regulatory Status:

The U.S. 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 cells are included in these regulations.

Medical Policy Statement

The safety and efficacy of specified bone marrow/hematopoietic cell transplants for plasma cell dyscrasias, including multiple myeloma, plasma cell leukemia, plasmacytoma, and POEMS syndrome, have been established. They may be considered useful therapeutic options for individuals meeting specified guidelines.

Inclusionary and Exclusionary Guidelines

MULTIPLE MYELOMA

Inclusions:

The following hematopoietic cell transplantations for multiple myeloma including plasma cell leukemia and plasmacytoma are considered established:

- Single or second (salvage - refers to treatments used after a condition has not responded to standard therapy) *autologous* hematopoietic cell transplantation.
- Tandem transplant with or without maintenance therapy can be considered for **any** of the following:
    - All individuals who are candidates for hematopoietic cell transplantation; **or**
    - Individuals who do not achieve at least a very good partial response (VGPR) after the first autologous hematopoietic cell transplantation [A very good partial response, as defined by the International Myeloma Working Group [IMWG] is a serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hr. (Revised based on the new criteria by IMWG); **or**
    - Individuals with high-risk features.
- Tandem transplantation with an initial round of *autologous* hematopoietic cell transplantation followed by a non-marrow-ablative conditioning regimen and *allogeneic* hematopoietic cell transplantation to treat individuals of newly diagnosed multiple myeloma.
- Myeloablative or nonmyeloablative *allogeneic* hematopoietic cell transplant is an acceptable option in patients with responsive or primary progressive disease as salvage therapy when these individuals have undergone *a prior autologous* hematopoietic cell transplant
- Allogeneic HCT should be considered appropriate therapy for any eligible individual with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT.

Exclusions:

- *Allogeneic hematopoietic cell transplantation*, myeloablative or nonmyeloablative, as initial therapy of newly diagnosed multiple myeloma is considered experimental/investigational.
- More than two tandem transplants, two single transplants, or a single and a tandem transplant per individual for the same condition.
- The routine harvesting or storage of an individual's umbilical cord blood for possible use at some unspecified time in the future.

POEMS SYNDROME

Inclusions:

Autologous hematopoietic cell transplantation to treat disseminated POEMS syndrome.

Exclusions:

Allogeneic and tandem hematopoietic cell transplantation to treat POEMS syndrome.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38206	38207	38208	38209
38210	38211	38212	38213	38214	38215
38230	38232	38240	38241	38242	S2140
S2142	S2150				

Other codes (investigational, not medically necessary, etc.):

0337U

Note: Some code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Potential Contraindications For Transplant:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).
- Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

Rationale

NEWLY DIAGNOSED MULTIPLE MYELOMA

Risk-Adapted Therapy

The approach to the treatment of newly diagnosed multiple myeloma (MM; symptomatic) is dictated by eligibility for autologous hematopoietic cell transplantation (HCT) and risk-stratification.(13) Risk stratification, using fluorescent in situ hybridization and conventional karyotyping divides patients into high- or standard-risk categories.

High-risk patients, which comprise approximately 25% of patients with MM, are defined by any of the following cytogenetic findings: 17p deletion, translocations of chromosomes 4 and 14, chromosomes 14 and 16, chromosomes 14 and 20, or a 1q gain.(15) Standard-risk patients are those with hyper diploidy (translocations of chromosomes 11 and 14 and chromosomes 6 and 14).

High-risk patients are generally treated with a bortezomib-based induction followed by autologous HCT and then bortezomib-based maintenance.(15) Standard-risk patients are typically treated with bortezomib-based induction therapy followed by autologous HCT and then maintenance with lenalidomide; however, if the patient is tolerating the induction regimen well, an alternative strategy is to continue the initial therapy after hematopoietic stem cell collection, reserving the transplant for first (relapse – return of disease after a period of improvement).

Autologous HCT vs Standard Chemotherapy

Clinical Context and Therapy Purpose

The purpose of autologous HCT as initial treatment in individuals who have newly diagnosed MM is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with newly diagnosed MM.

Interventions

The therapy being considered is autologous HCT as initial treatment.

Comparators

The following therapies are currently being used to make decisions about newly diagnosed MM: conventional chemotherapy with or without novel therapies.

Outcomes

The general outcomes of interest are overall survival (OS) and treatment-related morbidity.

Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials
Several RCTs have compared autologous HCT with treatment regimens that utilize newer MM agents. Richardson et al (2022) conducted a US-based, multicenter, open-label RCT comparing lenalidomide, bortezomib, and dexamethasone alone with the lenalidomide, bortezomib, and dexamethasone regimen in addition to autologous HCT plus melphalan in patients with newly diagnosed multiple myeloma.(66) All patients received daily maintenance lenalidomide until disease progression, unacceptable toxicity, or withdrawal from treatment or the trial. Patients treated with chemotherapy alone (n=357) had lower median PFS (46.2 months) compared with those who received chemotherapy and autologous HCT (n=365; 67.5 months). Patients who received chemotherapy only had higher rates of disease progression or death at a median follow-up of 76 months (HR, 1.53; 95% CI, 1.23 to 1.91; p<.001). Overall survival was similar between groups. Grade 3 or higher treatment-related adverse events were higher in patients undergoing HCT (94.2% vs. 78.2%).

Cavo et al (2020) conducted a multicenter, randomized, open-label phase 3 study comparing standard-dose intensification therapy with bortezomib, melphalan, and prednisone (n=495) to high-dose melphalan plus autologous HCT (n=702) in patients with newly diagnosed MM (up to 65 years of age).(16) Within the autologous HCT group, 492 received a single autologous HCT and 210 received a double autologous HCT. Median progression-free survival (PFS) was 56.7 months (95% confidence interval [CI], 49.3 to 64.5) for patients receiving autologous HCT versus 41.9 months (95% CI, 37.5 to 46.9) for those assigned to standard-dose intensification therapy (hazard ratio, 0.73; 95% CI,0.62 to 0.85; p=.0001). The 5-year OS rate was 75.1% (95% CI, 71.7 to 78.5) for patients in the autologous HCT group and 71.6%(95% CI, 67.4 to 76.1) for those in the standard-dose intensification therapy group (hazard ratio, 0.90; 95% CI, 0.71 to 1.13; p=.35).Among patients with high-risk cytogenetic profiles, OS was significantly better with autologous HCT.

Attal et al (2017) conducted a randomized, open-label phase 3 trial in patients less than 65 years of age with newly diagnosed MM.(17) Patients were randomly assigned to receive consolidation therapy with 5 cycles of bortezomib, lenalidomide, and dexamethasone(n=350) or high-dose melphalan followed by autologous HCT and 2 cycles of bortezomib, lenalidomide, and dexamethasone (n=350).With a median follow-up of 43 months, median PFS was 36 months in the non-transplant group versus 50 months in the transplant group (hazard ratio, 0.65; p<.001). The 4-year PFS rates were 35% and 50% for non-transplant and transplant groups respectively(p<.001), while 4-year OS rates were 82% and 81%, respectively (p=.43). Median OS was not reached for either group.

An RCT by Gay et al (2015) compared autologous HCT to standard chemotherapy plus lenalidomide.(18) The open-label RCT from 59 centers in Europe and Australia used a 2x2 factorial design to compare four groups 1) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide alone, 2) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide and prednisone 3) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide alone, and 4) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide plus prednisone. The primary outcome was progression-free survival (PFS). Mean follow-up at the time of publication was 52 months. Median PFS was superior for the HCT group plus standard consolidation (43.3 months, 95% CI 33.2-52.2 months) compared to chemotherapy plus lenalidomide (28.6 months, 95% CI 20.6-36.7 months; p<.0001). The rate of grade III or IV adverse events was higher for the HCT group than for the chemotherapy groups (hematological events, 84% vs 26%, gastrointestinal complications, 20% vs 5%; infections, 19% vs 5%; all respectively).

Based on several prospective, randomized trials comparing conventional chemotherapy to high-dose therapy plus autologous HCT for patients with multiple myeloma, autologous HCT has become the treatment of choice in patients younger than 65 years of age.

Data from seven randomized studies are available.(19-25) In all but 1 study (Barlogie et al [2006]),(21) the complete response (CR) rate was superior in the high-dose chemotherapy plus autologous HCT arm. The Barlogie study published final results from the phase III S9321 trial, which was initiated in 1993 and randomized 516 patients with MM to standard therapy or to myeloablative conditioning with melphalan 140 mg/m^2 plus total body irradiation followed by autologous HCT. These trialists reported virtually no difference in outcomes, including response rates, progression-free survival (PFS), and OS. In five of the seven studies, the superior CR rate translated into a significant increase in PFS. However, in the 2 studies that did not show an improved PFS with autologous HCT, randomization was not performed at diagnosis but only after induction treatment, possibly introducing selection bias.(19) Three of the seven studies showed superior OS in the autologous HCT group.(20,23,25)

The Intergroupe Francophone du Myélome (IFM) showed the superiority of high-dose chemotherapy plus autologous HCT compared with conventional chemotherapy in a 1996 randomized trial of 200 patients younger than 65 years of age.(20) The group that underwent autologous HCT had significantly improved response rates, event-free (EFS), and overall survival. Seven years later, the British Medical Research Council published similar results.(23)

Systematic Reviews

A systematic review and meta-analysis by Mian et al (2020) specifically sought to examine the impact of autologous HCT in patients aged 65 years or older with newly-diagnosed MM.(26) This review included data from 2 RCTs and 6 observational studies. In a pooled analysis of the observational studies, autologous HCT was associated with favorable effects on OS compared to non-HCT therapy (hazard ratio, 0.44; 95% CI, 0.34 to 0.58; p<.0001). However, in the pooled analysis of RCT data, the impact of autologous HCT on OS was uncertain (hazard ratio, 0.94; 95% CI, 0.25 to 3.54, p=.93). Observational data also showed higher CR rates with autologous HCT (odds ratio, 5.06; 95% CI, 2.60 to 9.88; p<.0001). The authors of the review concluded that autologous HCT may improve the OS and CR rates in elderly patients based on observational data, but the quality of the evidence is very low and more studies are needed.

A systematic review by Koreth et al (2007) of 2,411 patients enrolled in randomized controlled trials (RCTs) compared standard-dose chemotherapy to myeloablative chemotherapy plus single autologous HCT.(27) Meta-analysis concluded that myeloablative therapy with autologous HCT increased the likelihood of progression-free survival (PFS) (hazard ratio [HR] of progression: 0.75; 95% confidence interval [CI]: 0.59–0.96) but not overall survival (OS) (HR of death, 0.92; 95% CI: 0.74–1.13); in this group, the odds ratio for treatment-related mortality (TRM) was 3.01 (95% CI: 1.64–5.50). However, the effects of myeloablative chemotherapy and autologous HCT may have been underestimated because up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HCT as salvage therapy when multiple myeloma progressed. This could account for the lack of a significant difference in OS between the two groups.

Retrospective Studies
Marini et al (2019) published a retrospective study of elderly (age ≥65 years) MM patients treated with autologous stem cell transplantation (ASCT) at a single Portuguese center between 2010 and 2016.(28) The median follow-up for ASCT (n=132) patients and controls (n=23), who did not receive transplantation, was 30 months. The overall transplant-related mortality rate was 3.8%, and ASCT had a higher survival rate than the control group (OS 59 and 30 months, respectively, p=.037; event-free survival 45 and 27 months, respectively, p=.014). The study was limited by its retrospective nature, lack of randomization, and the subjective categorization for transplant of patients.

Subsection Summary: Autologous HCT vs Standard Chemotherapy
For individuals with newly diagnosed MM, evidence from multiple RCTs has suggested that high-dose chemotherapy with autologous HCT is superior to standard chemotherapy in PFS, and possibly OS. More recent RCTs comparing high-dose melphalan plus autologous HCT to chemotherapy regimens that include novel agents have also shown that high-dose melphalan plus autologous HCT improves PFS.

Tandem Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose
The purpose of tandem autologous HCT in individuals who have newly diagnosed MM is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with newly diagnosed MM.

Interventions
The therapy being considered is tandem autologous HCT. Tandem HCT involves an autologous transplant followed by a preplanned second transplant, either another autologous or reduced-intensity conditioning (RIC) allogeneic transplant. A tandem transplant differs from a second salvage transplant in that a tandem transplant involves prospective planning for a second transplant at the time the first transplant is being planned.

Comparators
The following therapies are currently being used to make decisions about newly diagnosed MM: conventional chemotherapy with or without novel therapies.

Outcomes
The general outcomes of interest are OS and treatment-related morbidity.

Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles detailed above.

Review of Evidence

Tandem Autologous Hematopoietic Cell Transplantation

Randomized Controlled Trials
The first randomized trial of tandem autologous transplants (IFM-94) was published in 2003 by Attal et al.(29) This trial randomized patients with newly diagnosed myeloma to single or tandem autologous transplants. Outcomes were analyzed by intent-to-treat (ITT) at 75 month follow-up. Among those randomized to single transplants (n=199), 148 relapsed: 33 were salvaged with a second auto-transplant, 13 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Among those randomized to tandem auto-transplants (n=200), 129 patients experienced disease relapse: 34 received salvage therapy with another (third) transplant, 12 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Seven years after diagnosis, patients randomized to tandem transplants had higher probabilities than those randomized to single transplants for event-free (EFS; 20% vs. 10%; p=.03), relapse-free (RFS; 23% vs. 13%, respectively; p<0.01), and overall survival (OS; 42% vs. 21%; p=.010) all respectively. Treatment-related mortality (TRM) was 6% and 4% after tandem and single transplants, respectively (p=.40). Second transplants extended survival only for those who failed to achieve a CR or very good partial response (VGPR) after one transplant (OS at 7 years: 43% vs. 11%, respectively; p<.001).

An accompanying editorial by Stadtmauer (2003) raised concerns that IFM-94 results might be specific to the regimens used for myeloablative therapy.(30) Patients in the single transplant arm received melphalan 140 m/m^2 plus total-body irradiation (TBI), while those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. The editorial cites an IFM-95 study as evidence, suggesting melphalan 140 mg/m^2 plus TBI may be less effective and more toxic than myeloablative therapy plus melphalan 200 mg/m^2 and no TBI. Based on this, the editorialists hypothesized that increased survival in the IFM-94 tandem arm may have resulted from greater cumulative exposure to melphalan (280 mg/m^2 vs.140 mg/m^2).

The Prospective, Randomized Study of Single Compared With Double Autologous Stem-Cell Transplantation for Multiple Myeloma(Bologna 96) clinical study (2007) assessed single and double autologous HCT (n=321).(31) Patients undergoing tandem autologous HCT were more likely than those with a single autologous HCT to attain at least a near CR (47% vs. 33%; p=.008), to prolong RFS (median, 42 vs. 24 months; p<.001), and extend EFS (median, 35

months vs. 23 months; p=.001), all respectively. There was no significant difference between the groups in TRM (3–4%). There was a trend for improved OS among patients in the double-transplantation group (7-year rate of 60%), compared with the single-transplant group (7-year rate of 47%; p=.10). Conversely, among patients achieving CR or near CR after one transplant, EFS and OS estimates did not significantly different according to transplant(s) received by study randomization. A subgroup analysis of outcomes of patients assigned to the two treatment arms, conducted by treatment response, showed that the benefit of a second transplant was particularly evident in patients who failed at least near CR after the first autologous transplant.

In the RCT by Cavo et al (2020) described in the section above, patients who were assigned to receive autologous HCT at a center that performed double autologous HCT were randomly assigned to receive either single (n=209) or double (n=210) autologous HCT.(16) Outcomes were compared between these subgroups in a secondary analysis. Double autologous HCT significantly improved rates of 5-year PFS (53.5% vs. 44.9%; hazard ratio, 0.74; 95% CI, 0.56 to 0.98; p=.036) and 5-year OS (80.3% vs. 72.6%; hazard ratio, 0.62; 95% CI, 0.41 to 0.93; p=.022) compared to single autologous HCT. Patients with high-risk cytogenetic profiles appeared to attain a greater magnitude of benefit with double HCT versus single HCT, compared to patients with standard-risk profiles.

Stadtmauer et al (2019) reported a randomized phase 3 study in patients with symptomatic MM who received at least 2 cycles of any regimen as initial systemic therapy without disease progression and who were within 2 to 12 months of the first dose of initial therapy.(32) Patients were randomly assigned to 1 of 3 treatment arms: autologous HCT (n=257), tandem autologous HCT (n=247), or autologous HCT plus 4 cycles of lenalidomide, bortezomib, and dexamethasone (n=254). Rates of 38-month PFS were similar across groups (58.5%, 57.8%, and 53.9% for tandem HCT, autologous HCT plus lenalidomide/bortezomib/dexamethasone, and autologous HCT respectively), as were rates of 38-month OS (81.8%, 85.4%, and 83.7%, respectively). However, 32% of patients in the tandem group did not receive the second HCT. Results of this study differed from those of the Cavo et al study described above. This may be related to differences in initial therapy; in the Cavo et al study, patients received a prespecified number of induction therapy cycles that did not include immunomodulatory agents (e.g., lenalidomide), while the majority of patients in this study received immunomodulatory agents as part of their initial therapy prior to transplant. Additionally, more patients in the Cavo et al study underwent tandem HCT as assigned (only 20% did not receive the second transplant).(16)

Retrospective Study

Villalba et al (2022) analyzed data from 35 hospitals in the Spanish Myeloma Group.(67) Patients (N=213) with newly diagnosed multiple myeloma and high-risk cytogenetics underwent single (n=142) or tandem (n=71) autologous HCT. At a median follow-up of 31 months, PFS was nonsignificantly longer with tandem HCT compared with single HCT (48 vs. 41 months; p=.33). Patients receiving tandem HCT were younger, had more advanced stage disease, and a higher plasma cell infiltration at diagnosis. More patients in the singe-transplant group died by the time of analysis than those undergoing tandem transplant although this was not statistically significant (23% vs. 12.7%; p=.09). The authors concluded that tandem HCT partly overcomes the poor prognosis of high-risk cytogenetics when compared with a single HCT but noted further study is needed.

Subsection Summary: Tandem Autologous HCT
Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improves OS and recurrence-free survival in newly diagnosed MM. Two recent RCTs found conflicting results on the benefit of tandem autologous HCT versus single autologous HCT; however, the study that found no additional benefit with tandem autologous HCT had a higher rate of nonadherence to the second planned HCT. Differences in initial therapy regimens between trials may also have led to conflicting results.

Tandem Autologous HCT Followed by Reduced-intensity Conditioning (RIC) Allogeneic HCT

Randomized Controlled Trials
Several trials have evaluated RIC allogeneic HCT (allo-HCT) following a single or tandem autologous HCT. These trials were based on “genetic randomization,” ie, patients with a human leukocyte antigen (HLA)-identical sibling who were offered RIC allogeneic HCT following the autologous HCT, whereas the other patients underwent either single or tandem autologous transplants.

The first published study by Garban et al (2006), included high-risk patients.(33) Sixty-five patients were in the autologous followed by RIC allogeneic group and 219 in the tandem autologous (autologous plus autologous) HCT group. Based on the intention-to-treat analysis, there was better median EFS and OS in the tandem autologous HCT group than in the RIC allo-HCT group (35 months versus 31.7; p-value= not significant and 47.2 months versus 35; p=.07, respectively). If results for only those patients who actually received the autologous HCT followed by RIC allogeneic-HCT (n=46) or tandem autologous HCT (n=166) were analyzed, the superior OS was again seen in the tandem autologous group (median 47.2 months vs. 35 months; p=.07). Updated results of this population were reported by Moreau et al (2008).(34) Comparing the results of the 166 patients who completed the whole tandem autologous HCT protocol to the 46 patients who underwent the entire autologous followed by RIC allogeneic program, no difference was seen in median EFS (25 months vs. 21 months, respectively; p=.88), with a trend toward superior median OS in favor of double autologous HCT (57 months vs. 41 months, respectively; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

A study by Bruno et al (2007) included 80 patients with an HLA-identical sibling who were allowed to choose allografts or autografts for the second transplant (58 completed an autograft or allograft sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence).(35) Results among those completing tandem transplantation showed a higher CR rate after the second transplant for the autologous plus allo-HCT group (55%) than for the tandem autologous HCT group (26%; p=.004). Additionally, EFS and OS were superior for the patients who underwent autologous plus allogeneic transplantation than for the tandem autologous transplantation (35 months vs. 29 months; p=.02 and 80 months vs. 54; p=.01, respectively). Comparing the group with HLA-identical siblings and those without, in a pseudo intention-to-treat analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The treatment-related mortality rate at 2 years was 2% in the tandem autologous group and 10% in the autologous plus allogeneic group; 32% of the latter group had extensive, chronic GVHD.

Rosinol et al (2008) reported the results of a prospective study of 110 patients with MM who failed to achieve at least near-complete remission after a first autologous HCT and were scheduled to receive a second autologous transplant (n=85) or an RIC allogeneic transplant (n=25), depending on the availability of an HLA-identical sibling donor.(36) The autologous followed by RIC-allogeneic group had a higher CR rate (40% vs. 11%, respectively; p=.001) and a trend toward a longer median PFS (31 months vs. not reached, respectively; p=.08). There were no statistical difference in EFS or OS estimates between groups. The autologous followed by RIC-allogeneic group experienced a higher transplantation-related mortality rate (16% vs. 5%, respectively; p=.07) and had a 66% chance of chronic GVHD.

Although the results differed between the Garban (2006) and the Moreau (2008) studies (33,34) and the Bruno (2007) and Rosinol (2008) studies,(35,36) these differences may have been due to study designs. The Moreau study focused on patients with high-risk disease and involved a conditioning regimen before the RIC-allogeneic transplant that may have eliminated some of the graft-versus-myeloma effect. Other contributing factors may have been non-uniform preparative regimens, different patient characteristics, and criteria for advancing to a second transplant (ie, only patients who failed to achieve a CR or near CR after the first autologous transplant underwent a second), and a small population in the allogeneic group in the Moreau study. Reviewers suggested that the subgroup of high-risk patients with de novo MM may have had equivalent or superior results with a tandem autologous HCT versus a tandem autologous plus RIC allogeneic HCT and that, in patients with standard-risk and/or chemo sensitive MM, RIC allograft may be an option.

An interim analysis of a prospective study by the European Group for Blood and Marrow Transplant (EBMT; 2008) was presented as a meeting abstract.(37) Previously untreated patients received vincristine, doxorubicin, dexamethasone (VAD) or VAD-like induction treatment, and had a response status of at least stable disease (ie, complete or partial remission or stable disease) at the time of autologous transplantation, which was also the time point for study inclusion. Patients with an HLA-identical sibling proceeded to RIC allo-HCT, while those without a matched sibling received no further treatment or a second autologous stem-cell transplant (if treated within a tandem program). A total of 356 patients were included, with a median follow-up of 3.5 years. Of these, 108 patients were allocated to the RIC allogeneic HCT group and 248 to the autologous transplant group. Of patients allocated to the allogeneic group, 98 received an RIC allogeneic transplant. At interim reporting, no significant difference in PFS or OS estimates were noted between groups.

Additional results from the EBMT trial were published by Gahrton et al (2013).(38) At 96 months, PFS and OS were 22% and 49% versus 12% (p=.027) and 36% (p=.030) for tandem autologous plus RIC allo-HCT versus autologous HCT, respectively. The corresponding relapse or progression rates were 60% and 82% (p<.001), respectively. Non-relapse mortality (NRM) rates at 36 months were 13% versus 3% (p<.001), respectively. In patients with the chromosome 13 deletion (del[13]), corresponding PFS and OS estimates were 21% versus 5% (p=.026) and 47% versus 31% (p=.154) respectively. Long-term outcome in patients with MM were better with autologous HCT followed by RIC-allogeneic HCT than with autologous HCT only, and the autologous followed by RIC-allogeneic approach seemed to overcome the poor prognostic impact of chromosome 13 deletion observed after autologous transplantation.

Krishnan et al (2011) conducted a phase III trial comparing tandem autologous HCT versus tandem autologous HCT plus RIC allo-HCT (tandem auto-allo group) in patients from 37 transplant centers in the U.S., who between 2003 and 2007, had received an autologous HCT (n=710).(39) Of these patients, 625 had standard-risk disease and 156 (83%) of 189 patients in the tandem auto-allo group and 366 (84%) of 436 in the tandem autologous group received a second transplant. Patients were eligible for transplantation if they were younger than 70 years of age and had completed at least three cycles of systemic therapy for myeloma within the past 10 months. Patients were assigned to receive a second autologous or allogeneic HCT based on the availability of an HLA-matched sibling donor. Patients in the tandem autologous group were subsequently randomized to observation (n=219) or maintenance therapy with thalidomide plus dexamethasone (n=217). Kaplan-Meier estimates of 3-year PFS were 43% (95% CI, 36 to 51) in the tandem auto-allo group and 46% (95% CI, 42% to 51%) in the tandem autologous group (p=.67). The OS also did not differ at 3 years (77% [95%, CI, 72 to 84] vs 80% [CI, 77 to 84]; p=.19). Grade 3, 4 or 5 morbidity rates between the 2 groups were 46% and 42%, respectively. The data suggest nonmyeloablative tandem auto-allogeneic HCT was no more effective than tandem autologous HCT for patients with standard-risk myeloma.

Retrospective Studies
Maffini et al (2018) published long-term follow-up results for MM patients treated with tandem autologous-allogeneic HCT.(40) The study consisted of 209 patients (86%) who received tandem HCT upfront and 35 patients (14%) who received tandem HCT after failing a previous autologous HCT. Median follow-up was 8.3 years. Five-year OS and PFS were 54% (95% CI, 48% to 60%) and 31% (95% CI, 25% to 36%), respectively; 10-year OS and PFS were 41% (95% CI, 34% to 48%) and 19% (95% CI, 13% to 24%), respectively. Overall non-relapse mortality was 2% at 100 days and 14% at 5 years.

Subsection Summary: Tandem Autologous HCT Followed by RIC Allo-HCT
Although the body of evidence has shown inconsistencies in terms of OS and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allo-HCT, although at a cost of higher TRM compared with conventional treatments.

Allogeneic Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose
The purpose of allo-HCT as initial treatment in individuals who have newly diagnosed MM is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with newly diagnosed MM.

Interventions
The therapy being considered is allo-HCT as initial treatment.

Comparators
The following therapies are currently being used to make decisions about newly diagnosed MM: conventional chemotherapy with or without novel therapies.

Outcomes
The general outcomes of interest are OS l and treatment-related morbidity.

Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles detailed above.

Narrative Reviews
The role of allo-HCT remains controversial, in particular, because of conflicting data from cooperative group trials, but also because of improvement in outcomes with proteasome inhibitors, new immune-modulatory agents, and the use of posttransplant maintenance therapy. These issues were reviewed and summarized in 2013 and 2014.(41,42)

Although myeloablative allogeneic HCT may be the only curative treatment in MM (due to its graft-versus-myeloma effect), its use has been restricted to younger patients. Even with the limited indications, the toxicity-related death rate for infections and GVHD is high, and this strategy has been almost completely abandoned.(43)

In an approach to reduce non-relapse mortality associated with allogeneic HCT, nonmyeloablative conditioning (RIC) methods have been investigated. Most studies are phase II, with no comparison to other treatment modalities. One retrospective study compared myeloablative and non-myeloablative conditioning.(44) This study, conducted by the EBMT, found that transplant-related mortality was significantly reduced with RIC but because of a higher relapse or progression rate, there was no significant improvement in OS.

When RIC-allogeneic HCT alone is used in patients with a high tumor burden or with chemotherapy-resistant disease, the immunologic effect of the graft is not sufficient to preclude relapses.(45) Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HCT.(43)

Section Summary: Allo-HCT
Studies have reported on patients with both myeloablative conditioning and RIC. Limitations of the published evidence include patient sample heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes, and inconsistency in reporting or collecting outcomes. Nonmyeloablative allo-HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allo-HCT improves survival better than autologous HCT.

RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Salvage Autologous Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose
The purpose of autologous HCT in individuals who have relapsed MM after failing an autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with relapsed MM after failing an autologous HCT.

Interventions
The therapy being considered is autologous HCT.

Comparators
The following therapies are currently being used to make decisions about relapsed MM: conventional chemotherapy with or without novel therapies. Despite improved survival rates with autologous HCT versus conventional chemotherapy, many patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HCT include regimens utilizing newer agents (e.g., daratumumab- and bortezomib-based regimens), regimens utilizing traditional chemotherapy, or a second HCT.(15)

Outcomes
The general outcomes of interest are OS and treatment-related morbidity.

Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles detailed above.

Review of Evidence

Randomized Controlled Trials
Goldschmidt et al (2020) conducted a randomized, open-label, multicenter phase 3 study (the ReLApsE trial) in patients aged 18 to 75years with a first to third relapse of MM.(46) These patients had previously undergone autologous HCT and attained remission of at least 12 months prior to relapse. Patients were randomized to receive a repeat autologous HCT (n=139) or continuous therapy with lenalidomide plus dexamethasone (n=138). Patients who underwent repeat autologous HCT also received reinduction therapy with lenalidomide plus dexamethasone, salvage high-dose chemotherapy with melphalan, and lenalidomide maintenance. In the primary ITT analysis, no significant differences were seen in PFS (median, 20.7 months vs. 18.8 months for transplant vs. control; hazard ratio, 0.87; 95% CI, 0.65 to 1.16; p=.34) or OS (median not reached in the transplant group vs. 62.7 months in the control arm; hazard ratio, 0.81; 95% CI, 0.52 to 1.28; p=.37). However, only 71% of patients assigned to the transplant group actually underwent salvage high-dose chemotherapy and autologous HCT. Post hoc analyses found that the patients who received salvage high-dose chemotherapy and autologous HCT had a trend toward superior PFS compared to the control group, and statistically superior OS (median not reached vs. 57 months; hazard ratio, 0.56; 95% CI, 0.32 to 0.99; p=.046).

Cook et al (2014) conducted a multicenter, randomized, open-label, phase III study involving 51 centers across the United Kingdom, with enrollment occurring between 2008 and 2012.(47) Inclusion criteria were patients at least 18 years old with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT. Before randomization, eligible patients received bortezomib, doxorubicin, and dexamethasone induction therapy and then underwent peripheral blood stem cell mobilization and harvesting, if

applicable. Eligible patients were randomized (1:1) to high-dose melphalan 200 mg/m^2 plus salvage autologous HCT or oral cyclophosphamide 400 mg/m^2/wk for 12 weeks. The primary end point was time to disease progression, analyzed by intention to treat. A total of 297 patients were enrolled, of whom 293 received induction therapy. Among the latter, 174 patients with sufficient harvest of peripheral blood stem cells were randomized to salvage HCT (n=89) or cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HCT group (19 months; 95% CI, 16 to 25 months) than in the cyclophosphamide group (11 months; 95% CI, 9 to 12 months; hazard ratio, 0.36 95% CI, 0.25 to 0.53; p<.001). Frequently reported (>10% of patients) grade 3 or 4 adverse events with induction, salvage HCT, and cyclophosphamide were: neutropenia (43% [125/293] patients receiving induction vs 76% [63/83] patients receiving salvage HCT group vs 13% [11/ 84] patients receiving cyclophosphamide), thrombocytopenia (51% [150/293] after induction vs 72% [60/83] with salvage HCT vs 5% [4/84] with cyclophosphamide), and peripheral neuropathy (12% [35/293] after induction vs none with salvage HCT or cyclophosphamide).

Final survival data for this trial were reported in 2016.(48) The HCT group had superior median overall survival (67 months, 95% CI 55 months to not estimable) compared to the chemotherapy group (52 months, 95% CI 42 to 60 months, p<.0001). Time to disease progression continued to favor the HCT group at the longer follow-up (19 months, [95% CI, 16 to 26 months] vs 11 months [95% CI 9 to 12 months], p=.02). There were no further adverse events related to the HCT procedure reported during longer follow-up. The cumulative incidence of second malignancies was 5.2% (95% CI 2.1-8.2%)

Retrospective Studies

A retrospective study by Ikeda et al (2019) examined outcomes of a second HCT (either allo-HCT [n=192] or repeat autologous HCT[n=334]) in patients with relapsed or progressive MM after a first autologous HCT.(49) Rates of 5-year OS were 23.8% after allo-HCT and 33.7% after repeat autologous HCT; however, differences in these rates were likely influenced by differences in baseline characteristics, such as age, performance status, time from initial HCT, and response to chemotherapy before HCT. Patients were assigned risk categories based on response to reinduction, performance status, and time from initial HCT; in intermediate-risk patients(the largest risk subgroup), OS rates were higher with repeat autologous HCT versus allo-HCT (28.2% vs. 21.5%; p<.004). No significant differences were noted in the low- and high-risk subgroups.

A multicenter retrospective study by Michaelis et al (2013) evaluated 187 patients drawn from the Center for International Blood and Marrow Transplantation who were treated with a second autologous HCT following relapse or progression of MM.(50) All but 12% of patients received a second autologous HCT 12 months or more after the initial transplantation; prior to a second autologous HCT, only 40% (n=74) of patients were in complete or partial response. In patients whose time from the first transplant to first relapse was greater than 36 months, investigators noted a decrease in the risk of relapse after a second autologous HCT(relative risk, 0.63; 95% CI, 0.49 to 0.97), and an increase in PFS and OS. For such individuals, the 3-year PFS rate was twice that of the cohort at large (26% vs 13%), and 5-year PFS rate (13%) was considerably superior to that of the larger group (5%). A comparison of OS rates showed a similar improvement: while the 5-year OS rate of 29% for the entire cohort was comparable to other studies of a second autologous HCT in relapsed MM, the 5-year OS rate for individuals with a time-to-relapse of 36 months or greater was considerably improved (48%; p=.026). After

3 years, only 4% (95% CI, 2% to 8%) of patients experienced NRM; however, relapse or disease progression was observed in 82% of patients after 3 years (vs 68% of patients with time-to-relapse ≥36 months after initial transplant). The investigators acknowledged a lack of data on maintenance regimens, cytogenetics, or staging of individual disease; they also noted that, during the observed time frame (1995-2008), several newer therapies were introduced, which were not accounted for during analysis. However, given findings similar to other retrospective studies during the same period, the investigators concluded that a second autologous HCT is an appropriate salvage therapy for eligible patients.

Qazilbash et al (2006) reported their experience with salvage autologous HCT or allo-HCT after a failed first autologous transplant.(51) Fourteen patients (median age, 52 years) received a second autologous transplant and 26 patients (median age, 51 years) underwent a RIC allo-HCT. The median interval between first and second transplants was 25 months for the autologous group and 17 months for the allogeneic group. After a median follow-up of 18 months (range, 2 to 69 months) for the autologous group, median PFS was 6.8months, and OS was 29 months. After a median follow-up of 30 months (range, 13 to 66 months) for the allogeneic group, median PFS was 7.3 months, and OS was 13 months. Univariate analysis in the allogeneic group found that an interval of more than 1 year between the first and salvage transplants predicted a significantly better OS (p=.02). None of the prognostic factors evaluated for the allogeneic group had a significant impact on survival in the autologous group (e.g., age, cytogenetics, type of donor, chronic GVHD).

Systematic Reviews

A review by Ziogas et al (2017) included studies of autologous HCT as salvage therapy in patients whose MM has relapsed following an initial autologous HCT (either single or tandem).(52) The primary aim of the review was to summarize the circumstances in which a second autologous HCT should be administered, especially as more regimens show potential as salvage or reinduction therapy, including anti-CD38 antibodies, next-generation proteasome inhibitors, or immunomodulatory drugs. The authors noted that most studies have been retrospective, or of small patient samples; however, in 15 of the included studies, more than 40 patients were evaluated. Overall response rates ranged from 55.3% to 97.4%; following a salvage transplant, median PFS across studies varied considerably (range, 8.5-40 months). The questions examined in the review concerned the safety and efficacy of a second autologous HCT, predictors of outcome and best maintenance approach following salvage autologous HCT, and the future of the treatment. Based on general agreement from studies that showed the particular benefit of salvage autologous HCT in patients with longer intervals from the first transplant to initial relapse, reviewers recommended that the treatment is administered to patients with remission of greater than 18 months following initial autologous HCT. Given heterogeneity across studies of novel maintenance therapies, reviewers called for more prospective studies, noting melphalan as a well-established basis for treatment.

In 2017, the EBMT reported on potential treatments for myeloma patients whose disease has relapsed following autologous stem cell transplantation; the included systematic review was primarily descriptive.(53) Among the treatments suggested were immunomodulatory drugs (ie, thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (ie, bortezomib, carfilzomib, ixazomib),monoclonal antibodies, and autologous HCT or allo-HCT. Reviewers noted that most of the studies of autologous HCT and allo-HCT are retrospective analyses of case series or data drawn from databases; to confirm the apparent benefits of transplantation over

chemotherapy alone, reviewers suggested that more prospective studies are needed for both types of procedure following relapse.

Section Summary: Salvage Autologous Hematopoietic Cell Transplantation
Despite some limitations of the published evidence, including patient sample heterogeneity, variability in treatment protocols, and short follow-up periods, the available trial evidence has suggested OS rates are improved with autologous HCT compared with conventional chemotherapy or continuous lenalidomide plus dexamethasone in this setting.

Tandem Autologous HCT for Relapse After First Autologous HCT

Clinical Context and Therapy Purpose
The purpose of tandem autologous HCT in individuals with refractory MM after failing a first HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with refractory MM after failing a first HCT.

Interventions
The therapy being considered is tandem autologous HCT.

Comparators
The following therapies are currently being used to make decisions about refractory MM: conventional chemotherapy with or without novel therapies.

Outcomes
The general outcomes of interest are OS and treatment-related morbidity.
Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles detailed above.

Review of Evidence

Systematic Reviews
A 2003 evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from four relevant clinical series.(54) Reviewers reported that some myeloma patients who relapsed after a first auto-transplant achieved durable complete or partial remissions after a second auto-transplant as salvage therapy. Factors found to increase the likelihood of durable remissions and extend survival included a chemosensitive relapse, younger age, a long disease-free or progression-free interval since the initial auto-transplant, and fewer chemotherapy regimens before the initial auto-transplant.

A review by McCarthy and Holstein (2016) summarized current treatment regimens for patients with myeloma who are eligible for autologous HCT or allo-HCT.(56) Following discussion of studies on induction, salvage, consolidation, and maintenance therapies, reviewers offered recommendations based on the available evidence. Based on 4 studies comparing autologous HCT with chemotherapy alone, reviewers recommended autologous HCT as standard of care for patients who are eligible; additionally, they recommended autologous HCT for the first relapse, based on the pooled hazard ratio of two studies showing a benefit in patients given autologous HCT following relapse (hazard ratio, 0.57; p=.037). Reviewers noted the increasing uncertainty regarding the efficacy and safety of allo-HCT compared with novel therapies; studies directly comparing allo-HCT with autologous HCT lack consistent results. However, RIC allo-HCT has been shown to have some benefit for patients whose disease is high-risk, especially in younger populations. As maintenance therapy, reviewers considered a number of studies evaluating thalidomide (n=8), which had conflicting results, as well as three randomized studies of lenalidomide, concluding that the latter treatment is standard of care.

Retrospective Studies
Olin et al (2009) reported their experience with 41 patients with MM who received a second salvage autologous HCT for relapsed disease. (55) The median time between transplants was 37 months (range, 3 to 91 months). The overall response rate in assessable patients was 55%. Treatment-related mortality was 7%. Median follow-up was 15 months, with a median PFS of 8.5 months and median OS of 20.7 months. In a multivariate analysis of OS, the number of prior lines of therapy (≥5) and time to progression after initial transplant were the strongest predictors of OS.

Section Summary: Tandem Autologous Hematopoietic Cell Transplantation for Relapse after First Autologous Hematopoietic Cell Transplantation
The evidence has shown tandem autologous HCT improves OS rates in this setting.

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) SYNDROME

Clinical Context and Therapy Purpose
The purpose of HCT in individuals with POEMS syndrome is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with POEMS syndrome.

Interventions
The therapy being considered is HCT.

Comparators
The following therapies are currently being used to make decisions about POEMS syndrome: conventional chemotherapy with or without novel therapies.

Outcomes
The general outcomes of interest are OS and treatment-related morbidity.

Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles detailed above.

Review of Evidence

Systematic Reviews
A 2012 Cochrane review published provides a comprehensive source on the treatment of POEMS.(57) Reviewers performed a broad literature search and identified no RCTs, no quasi-RCTs, no historically controlled trials and no trials with concurrent controls that met selection criteria. Reviewers selected 6 small series (total n=57 patients) evaluating autologous HCT. Two-year survival rates ranged from 94% to 100%. Pooled results suggested that TRM with autologous HCT would be 3 (2.7%) of 112. The reviewers cautioned that long-term outcomes with autologous HCT have not been evaluated and require continuing study.

A second 2012 review article found that case series suggested most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m^2.(5) Responses have been reported as durable but relapse occurs. Symptomatic progression has typically been reported as rare, with most progressions identified as rising vascular endothelial growth factor and radiographic. The reviewer also reported that long-term outcomes with autologous HCT are unclear given the sparse numbers. Findings were similar in an updated 2019 review by the same author.(8)

A review article by Autore et al (2017) evaluated potential mobilizing regimens for the collection of peripheral blood in patients with POEMS syndrome; reviewers also included a number of small studies evaluating the roles of vascular endothelial growth factor and lenalidomide in cases of POEMS syndrome.(58) In 7 studies using high-dose melphalan followed by autologous HCT, clinical response rates ranged from 69.3% to 100%, and morbidity rates related to autologous HCT ranged from 21.7% to 42.9%. Four studies evaluating lenalidomide as a treatment of POEMS syndrome showed clinical response rates ranging from 78% to 100%, although the case series included were small. Reviewers reported mixed results on the use of granulocyte colony-stimulating factor with chemo-mobilization compared with granulocyte colony-stimulating factor alone in 11 case series, in which engraftment syndrome occurred in 11% to 37.5% of patients when reported.

Case Series
A single-center series published in 2012 reported a 5-year OS of 94% and a PFS of 75% among 59 patients entered between 1999 and late 2011.(59) A second series (2014) included 9 patients with advanced POEMS syndrome who had an Eastern Cooperative Oncology Group performance status score of three or four and were treated with high-dose melphalan therapy followed by autologous HCT from 2004 to 2011.(60) Eight patients achieved an initial hematologic response, four of whom had complete responses. At a median follow-up of 44 months (range, 8-94 months), seven patients were alive, with three-year OS rate of 78%. There were no hematologic relapses in the survivors. One patient died of disease progression; the other died of pneumonia. All survivors improved in general performance status and clinical response. More recent single-center series publications including 36 to 95 patients show a 5 -year overall survival rate approximating 90%.

Retrospective Studies

In a retrospective, multicenter study, Cook et al (2017) evaluated 127 patients with POEMS syndrome who had received high-dose therapy (melphalan) and autologous HCT as first-line therapy; outcomes included transplant results, organ-specific response, OS, and PFS, and non-relapse mortality.(61) Engraftment was successful in most patients (96.8%); engraftment syndrome (n=29; 23%) did not appear significantly associated either with previous treatment (p<.018) or the inclusion of cyclophosphamide as a mobilizer (p=.590). Following transplantation, 48% of patients had achieved hematologic CR (n=49), 16 of whom were in a lower status preceding autologous HCT. At the three-year follow-up, the likelihood of relapse was 12% (95% CI, 5% to 18%); after five years, the likelihood of PFS was 74% (95% CI, 63.2% to 83.7%). Rates of NRM and OS after five years were also favorable: respectively, 7.7% (95% CI, 1.9% to 13.6%) and 88.6% (95% CI, 81.5% to 95.8%). The authors noted a significant association between a patient's performance score and PFS (p=.032), recommending that caregivers consider administering therapy before transplant to improve the performance score. A limitation of the study was that, although patients were treated between 1994 and 2010, newer imaging techniques were not reported, nor were vascular endothelial growth factor serum levels accounted for in the analysis.

Section Summary: POEMS Syndrome

There is a lack of RCT evidence on the use for HCT for POEMS syndrome, but cohort studies and case series have reported improvement in symptoms and disease progression after HCT. POEMS syndrome is rare and treatment options are few. Also, the natural history of POEMS does not suggest that spontaneous improvement will occur in the absence of treatment.

SUMMARY OF EVIDENCE

Newly Diagnosed Multiple Myeloma

For individuals who have newly diagnosed multiple myeloma (MM) who receive autologous hematopoietic cell transplantation (HCT) as initial treatment, the evidence includes randomized controlled trials (RCTs) that compared high-dose chemotherapy plus autologous HCT to standard chemotherapy regimens or regimens containing newer MM agents. Relevant outcomes are overall survival and treatment-related morbidity. In general, the evidence has suggested overall survival rates are improved with autologous HCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and inconsistency in reporting or collecting outcomes. Recent RCTs comparing high-dose chemotherapy plus autologous HCT to regimens that include novel MM agents have also shown that high-dose chemotherapy plus autologous HCT improves progression-free survival (PFS). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have newly diagnosed MM who receive tandem autologous HCT, the evidence includes several RCTs. Relevant outcomes are overall survival and treatment-related morbidity. Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improved OS and recurrence-free survival in newly diagnosed multiple myeloma. Two recent RCTs found conflicting results on the benefit of tandem autologous HCT versus single autologous HCT; however, the study that found no additional benefit with tandem autologous HCT had a higher rate of nonadherence to the second planned HCT. Differences in initial therapy regimens between trials may also have led to conflicting results. Several RCTs

compare reduced-intensity conditioning (RIC) allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on "genetic randomization," (ie, patients with a human leukocyte antigen-identical sibling were offered an RIC allo-HCT following autologous HCT, whereas other patients underwent either 1 or 2 autologous transplants). Although the body of evidence has shown inconsistencies in terms of overall survival and DFS rates, some studies have shown a survival benefit with tandem autologous HCT, followed by RIC allogeneic HCT, although at a cost of higher transplant-related mortality compared with conventional treatments. Factors across studies that may account for differing trial results include different study designs; nonuniform preparative regimens; different patient characteristics (including risk stratification); and criteria for advancing to a second transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have newly diagnosed MM who receive allo-HCT as initial myeloablative or nonmyeloablative conditioning as initial treatment, the evidence includes nonrandomized studies. Relevant outcomes are overall survival and treatment-related morbidity. Studies have reported on patients with both myeloablative and RIC conditioning. Limitations of the published evidence include patient sample heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and inconsistency in reporting or collecting outcomes. Nonmyeloablative allogeneic HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allogeneic HCT improves survival better than autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Relapsed or Refractory Multiple Myeloma
For individuals who have relapsed MM who receive autologous HCT after failing an autologous HCT, the evidence includes RCTs, retrospective studies and reviews summarizing recent studies on a second autologous HCT in relapsed myeloma. Relevant outcomes are overall survival and treatment-related morbidity. Despite some limitations of the published evidence, including patient sample heterogeneity, variability in treatment protocols, and short follow-up periods, the available trial evidence has suggested overall survival rates are improved with autologous HCT compared with conventional chemotherapy or continuous lenalidomide plus dexamethasone in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory MM after failing the first HCT, who receive tandem autologous HCT, the evidence includes a systematic review and a retrospective study. Relevant outcomes are overall survival and treatment-related morbidity. The evidence has shown tandem autologous HCT improves overall survival rates in this setting. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome
For individuals who have POEMS syndrome who receive HCT, the evidence includes retrospective cohort studies, case reports, and case series. Relevant outcomes are overall survival and treatment-related morbidity. No RCTs of HCT of any type have been performed in patients with POEMS syndrome of any severity, nor is it likely such studies will be performed because of the rarity of this condition. Available case reports and series are subject to

selection bias and are heterogeneous with respect to treatment approaches and peri-transplant support. However, for patients with disseminated POEMS syndrome, a chain of evidence and contextual factors related to the disease and MM, suggests improvement in health outcomes with autologous HCT. The evidence is sufficient to determine qualitatively that autologous HCT results in a meaningful improvement in the net health outcome.

Supplemental Information

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

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

In response to requests, BCBSA received input from 1 specialty medical society, 1 academic medical center, and 2 Blue Distinction Centers for Transplant while this policy was under review in 2017. There was consensus that allogeneic hematopoietic cell transplantation (HCT) is investigational for newly diagnosed multiple myeloma and as salvage therapy after primary graft failure and for primary progressive disease.

2013 Input

In response to requests, BCBSA received input from 3 academic medical centers and 6 Blue Distinction Centers for Transplant while this policy was under review in 2013. There was near-consensus that autologous HCT is medically necessary for POEMS syndrome, and near-consensus that allogeneic and tandem HCT is investigational for POEMS syndrome.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' 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.

American Society of Clinical Oncology

In 2019, the American Society of Clinical Oncology (ASCO) published practice guidelines for the treatment of multiple myeloma (MM).(62) The guidelines recommend offering up-front transplant to all eligible patients, although delayed HCT may be considered in select patients. Salvage or delayed HCT may be used as consolidation at first relapse in patients who choose not to proceed with HCT initially. Tandem autologous HCT and allogeneic HCT (allo-HCT) should not be routinely recommended. However, up-front tandem autologous HCT can be considered for select high-risk patients or those with a suboptimal response to the initial transplant; allo-HCT may be considered in select high-risk patients in the context of a clinical trial. For relapsed MM, autologous HCT, if not received after primary induction therapy, should

be offered to transplant-eligible patients. Repeat HCT may be considered in relapsed MM if progression-free survival after the first transplant was 18 months or greater.

American Society for Transplantation and Cellular Therapy
In 2015, the American Society for Blood and Marrow Transplantation (ASBMT; now referred to as the American Society for Transplantation and Cellular Therapy) published evidence-based guidelines on the use of HCT in patients with MM.(63) The ASBMT recognized that much of the evidence from randomized controlled trials summarized in the 2015 guidelines came from trials that predated the novel triple-therapy induction regimens. Furthermore, advances in supportive care and earlier disease detection have increasingly influenced decision making and allow individual tailoring of therapy. The ASBMT guidelines did not address POEMS or other plasma cell dyscrasias besides MM.

The ASTCT updated guidance for transplantation and cellular therapies in MM in 2022.(72) The panel endorsed continued use of autologous HCT for patients with newly diagnosed MM as a standard-of-care option, and did not recommend front-line use of allo-HCT and CAR-T outside the setting of a clinical trial. For patients not undergoing autologous HCT upfront, the panel recommended its use in first relapse. The panel also encouraged allo-HCT in relapsed/refractory MM setting only in the context of clinical trial.

The ASBMT, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group (2015) published joint guidelines based on an expert consensus conference.(64) These guidelines contained the following recommendations for HCT as salvage therapy:

<u>Autologous HCT</u>
- In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard.
- High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months.
- High-dose therapy and autologous HCT can be used as bridging strategy to allogeneic HCT.
- The role of post salvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, IMiDs, and oral proteasome inhibitors.
- Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short remission (less than 18 months).
- Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM relapsing after primary therapy comparing to “best non-HCT” therapy.”

<u>Allogeneic HCT</u>
- Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or

high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT.
- Whenever possible, allogeneic HCT should be performed in the context of a clinical trial.
- The role of post allogeneic HCT maintenance therapy needs to be further explored.
- Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.

In 2020, the ASTCT published a guideline on indications for HCT and immune effector cell therapy.(73) Regarding plasma cell dyscrasias, the guideline states that MM remains the most common indication for autologous HCT. For rarer plasma cell dyscrasias like POEMS syndrome, autologous HCT may be considered a clinical option on the basis of single-center and registry data. Detailed recommendations in adults can be found in Table 2.

Table 2. Summary of Recommendations for Hematopoietic Cell Transplantation in Plasma Cell Disorders Including Multiple Myeloma and POEMS Syndrome

Indication	Allogeneic HCT	Autologous HCT
Myeloma, initial response	D	S
Myeloma, sensitive relapse	S	S
Myeloma, refractory	C	C
POEMS syndrome	N	C
Relapse after autologous transplant	C	C

C: standard of care, clinical evidence available; D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care

International Myeloma Working Group

The 2010 conclusions and recommendations on the current status of allogeneic HCT for MM are as follows: Myeloablative allogeneic HCT may cure a minority of patients, but is associated with a high transplant-related mortality, but could be evaluated in well-designed prospective clinical trials.(65) Nonmyeloablative allogeneic HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse and convincing evidence is lacking that allo-HCT improves survival as compared with autologous HCT.

National Comprehensive Cancer Network

Autologous HCT:

The NCCN guidelines (v.4.2024) state that autologous HCT is the preferred option after induction therapy in transplant-eligible patients, but a delayed HCT after early stem cell collection and storage is appropriate as well (category 1 recommendation).(69) A repeat HCT can be considered for refractory/progressive disease after primary treatment in patients with prolonged response to initial HCT.

Tandem hematopoietic cell transplant:

The NCCN recommends collecting enough stem cells for 2 transplants in younger patients if tandem transplant or salvage transplant would be considered.(69) A tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for HCT

and is an option for patients who do not achieve at least a very good partial response after the first autologous HCT and those with high-risk features.

Allogeneic-HCT

The NCCN states the following for allo-HCT: "Allogeneic HCT includes either myeloablative or nonmyeloablative (ie, "mini" transplant) transplants. Allogeneic HCT has been investigated as an alternative to autologous HCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population".(69)

POEMS Syndrome

The NCCN guidelines recommend autologous HCT in patients with POEMS syndrome who are eligible as sole therapy or as consolidation therapy after induction therapy.(69)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01208662[a]	A Randomized Phase III Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib, and Dexamethasone (RVD) to High-dose Treatment With Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients up to 65 Years of Age	660	Sep 2025
NCT05675319	Allogeneic Stem Cell Transplantation vs. Conventional Therapy as Salvage Therapy for Relapsed / Progressive Patients With Multiple Myeloma After First-line Therapy	482	Mar 2023
Unpublished			
NCT02322320	Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 (BMT CTN #Q07LT)	273 (actual enrollment)	Jun 2019 (completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations
National:

Decision Memo for Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, and Sickle Cell Disease) (CAG-00444R) – January 2016 (71)

The Centers for Medicare & Medicaid Services (CMS) modified their existing National Coverage Determinations Manual to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for multiple myeloma as follows:

MULTIPLE MYELOMA
CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with multiple myeloma (MM) using the Coverage with Evidence Development (CED) paradigm.

Allogeneic HSCT for multiple myeloma will be 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 who are participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS staging, Durie-Salmon staging, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage of allogeneic HSCT for multiple myeloma pursuant to CED must address the following question:

Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with multiple myeloma who receive allogeneic HSCT have improved outcomes as indicated by:

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

National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23) Effective Date: 3/06/24, Implementation Date: 10/7/24 (See determination for complete details) (70)

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Nationally Covered Indications

- **Autologous Stem Cell Transplantation (AuSCT)**
  - Effective October 2, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
    - Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
    - Adequate cardiac, renal, pulmonary, and hepatic function.

Nationally Non-Covered Indications

- ***Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)***
  - Effective for claims with dates of service on or after May 24, 1996, through January 26, 2016, allogeneic HSCT is not covered as treatment for multiple myeloma.
- **Autologous Stem Cell Transplantation (AuSCT)**
  - Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:
    - Up to October 1, 2000, multiple myeloma
    - Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias, Allogenic
- BMT – Autologous, for Malignant Astrocytomas and Gliomas, Autologus
- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma - Autologous and Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Tumors, Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 28, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/22/02	11/22/02	11/22/02	Joint medical policy established
3/19/04	3/19/04	3/26/04	Routine maintenance
4/11/05	4/11/05	4/11/05	Routine maintenance
1/1/07	11/1/06	10/20/06	Routine maintenance
11/1/07	11/2/07	10/30/07	Policy changed from investigational to established.
11/1/08	8/19/08	10/28/08	Routine maintenance
11/1/09	8/18/09	8/18/09	Routine maintenance
11/1/11	8/16/11	8/16/11	Policy title changed from “Allogeneic after Autologous Bone Marrow Transplant for Treatment of Multiple Myeloma (Tandem Transplant)” to “Bone Marrow/Stem Cell Transplant for Treatment of Multiple Myeloma.”
1/1/13	10/16/12	10/16/12	• Routine maintenance • Added “relative contraindications” to inclusionary/exclusionary section.
1/1/14	10/15/13	10/25/13	• Title changed to match BCBSA from former title, “BMT - Hematopoietic Stem-Cell Transplantation for Multiple Myeloma.” • Added information re: POEMS syndrome • Updated references and rationale. • No change to policy status.
3/1/15	12/12/14	12/29/14	• Routine maintenance. Updated references and rationale. No change in policy status.
3/1/16	12/10/15	12/10/15	Routine maintenance

3/1/17	12/22/16	12/27/16	• Routine maintenance. • Added CPT code 38207. • Added CMS decision memo information regarding coverage for allogeneic HSCT for MM.
3/1/18	12/12/17	12/12/17	• Routine maintenance • "Stem" removed "hematopoietic stem-cell transplantation" per NCCN change • Updated NCD 110.23 replaced 110.8.1
3/1/19	12/11/18		Routine maintenance
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance
1/1/23	12/2/22		Routine maintenance Updated 2nd bullet under Inclusion based on NCCN V1.2023 MM Tandem transplant with or without maintenance therapy can be considered for any of the following: • All patients who are candidates for hematopoietic cell transplantation; or • Patients who do not achieve at least a very good partial response (VGPR) after the first autologous hematopoietic cell transplantation [A very good partial response, as defined by the International Myeloma Working Group [IMWG] is a serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hr. (Revised based on the new criteria by IMWG); or

			• Patients with high-risk features. Added salvage definition under Inclusions section: (salvage - refers to treatments used after a condition has not responded to standard therapy) Added relapse definition under rationale section: relapse – return of disease after a period of improvement). (ky)
1/1/24	10/17/23		• Routine maintenance • Updated nomenclature for codes 38240, 38241, and 38242. • Based on requests received from Human Organ Transplant Program (HOTP) added plasma cell leukemia and plasmacytoma to the, Title, medical policy statement (MPS), Inclusions section, and to the Description/Background section. • Added this statement under the Inclusions section: Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT. • Vendor: N/A (ky)
1/1/25	10/15/24		• Minor Edits – updated patients to individuals in MPS and Inclusions/Exclusions section.

			• Routine maintenance • Updated nomenclature for code S2150 • Vendor: N/A (ky)

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR PLASMA CELL DYSCRASIAS, INCLUDING MULTIPLE MYELOMA, PLASMA CELL LEUKEMIA, PLASMACYTOMA, AND POEMS SYNDROME

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier II coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier II coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.