Policy Statement

Multiple Myeloma
A single or second (salvage) autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma.

Tandem autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma in patients who fail to achieve at least a near-complete or very good partial response after the first transplant in the tandem sequence. (For definitions of near-complete response and very good partial response, see Policy Guidelines section).

Tandem transplantation with an initial round of autologous hematopoietic cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic stem cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered medically necessary to treat newly diagnosed multiple myeloma patients.

Allogeneic hematopoietic cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered investigational.

POEMS Syndrome
Autologous hematopoietic cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome (see Policy Guidelines section).

Allogeneic and tandem hematopoietic cell transplantation are considered investigational to treat POEMS syndrome.

Policy Guidelines

The International Working Group on Myeloma has updated the European Group for Blood and Marrow Transplant (EBMT) criteria to describe a complete response to multiple myeloma therapy. The criteria include negative immunofixation on the serum and urine; disappearance of soft tissue plasmacytomas; and 5% or fewer plasma cells in bone marrow aspiration.

In the Attal study, a very good partial response was defined as a 90% decrease in the serum paraprotein level.

In the Cavo study, near-complete response (nCR) was defined according to the response criteria proposed in 1998 by the European Group for Blood and Marrow Transplant (EBMT) as the disappearance of M protein at routine electrophoresis, but positive immunofixation.

Patients with disseminated POEMS syndrome may have diffuse sclerotic lesions or disseminated bone marrow involvement.

Coding
CPT grouped codes describing allogeneic and autologous hematopoietic cell therapy (HCT) services to the hematology section (CPT 38204-38242). Not all codes are applicable for each HCT procedure. For example, Plans should determine if cryopreservation is performed. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38207-38215).
The following CPT code describes cryopreservation and storage:

- **38207**: Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

The following codes describe thawing and washing of cryopreserved cells:

- **38208**: Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
- **38209**: Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

The following CPT codes describe certain cell types being depleted:

- **38210**: Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest; T-cell depletion
- **38211**: Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
- **38212**: Transplant preparation of hematopoietic progenitor cells; red blood cell removal
- **38213**: Transplant preparation of hematopoietic progenitor cells; platelet depletion
- **38214**: Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion

The following CPT code describes plasma cell concentration:

- **38215**: Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer

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**Description**

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. 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. In some cases, autologous or allogeneic hematopoietic cell transplantation (HCT) is considered as therapy.

**Related Policies**

- Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**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
Rationale

Multiple Myeloma
MM is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable. At diagnosis, most patients have the generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of disease complications.1,2,3

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 five years, approximately 3% per year for the next five years, and 1% for the next ten years.1,2

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, multiorgan 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 proinflammatory 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. Both major criteria and at least one of the minor criteria are necessary for diagnosis.7

| Table 1. Criteria and Associations for POEMS Syndrome |
|-----------------|-----------------|-----------------|-----------------|
| Major Criteria  | Minor Criteria  | Known Associations | Possible Associations |
| Polyneuropathy  | Sclerotic bone lesions | Clubbing | Pulmonary hypertension |
| Monoclonal plasma-proliferative disorder | Castleman disease | Weight loss | Restrictive lung disease |
| | Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy) | Thrombocytosis | Thrombotic diatheses |
| | Edema (edema, pleural effusion, ascites) | Polycythemia | Arthralgias |
| | Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) | Hyperhidrosis | Cardiomyopathy (systolic dysfunction) |
| | Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangioma, white nails) | | Fever |
| | Papilledema | | Low vitamin B12 levels |
| | | | Diarrhea |
The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000. Other large series had been described in the United States, and India. In general, patients with POEMS have superior overall survival compared with that of MM (nearly 14 years in a large series). However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported. Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, corticosteroids, alkylating agents, azathioprine, tamoxifen, trans-retinoic acid, and high-dose chemotherapy with autologous hematopoietic cell transplantation (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, are also under investigation.

HCT is a procedure in which hematopoietic stem cells are 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 a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in detail in Blue Shield of California Medical Policy: Placental and Umbilical Cord Blood as a Source of Stem Cells.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (except umbilical cord blood).

**Conditioning for HCT**

**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 of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include 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 graft-versus-host disease, which also increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability 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 space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, 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 graft-versus-host disease.

**Reduced-Intensity Conditioning Allo-HCT**

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy that are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of non-relapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For our purposes, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative as opposed to fully myeloablative (traditional) regimens.

**MM treatment overview**

In the prechemotherapy 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 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. 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. Novel agents such as the proteasome inhibitor bortezomib and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed and refractory myeloma and now have been integrated into first-line regimens. 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.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse
events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The earliest versions of this review were informed by 2 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessments in 1996 and 2 TEC Assessments in 1998. Since 1999, the treatment of multiple myeloma (MM) has changed radically. POEMS syndrome was added to this review in 2013.

Newly Diagnosed MM

Risk-Adapted Therapy

The approach to the treatment of newly diagnosed MM (symptomatic) is dictated by eligibility for autologous hematopoietic cell transplantation (HCT) and risk stratification.17 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: a 17p deletion; translocations of chromosomes 4 and 14, chromosomes 14 and 16, chromosomes 14 and 20; a chromosome 13 deletion; or hypodiploidy.17 Standard-risk patients are those with hyperdiploidy (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.17 Standard-risk patients are typically treated with non-alkylator-based therapy (e.g., lenalidomide plus low-dose dexamethasone) followed by autologous HCT; however, if the patient is tolerating the induction regimen well, an alternative strategy would be to continue the initial therapy after hematopoietic cell collection, reserving the transplant for the first relapse.

Recent reviews highlight the treatment of newly diagnosed myeloma (2011)18, as well as relapsed and refractory myeloma (2011).19 A 2011 review of the literature has highlighted advances in the use of autologous and allogeneic HCT (allo-HCT).20

Early vs Delayed HCT

A retrospective analysis by Dunavin et al (2017) compared survival and relapse rates in 167 patients who were treated for MM between 2002 and 2009 with induction therapy and autologous HCT.21 In the first group (n=102), autologous HCT was given no more than 12 months after diagnosis; in the second, autologous HCT was given 12 months or more after diagnosis, although individual reasons for later procedures were not specified. Following a standard induction therapy and preceding transplantation, more patients in the early group had achieved a complete response (CR) or very good partial response than in the late autologous HCT group (46% vs 62%, p=0.036). This difference remained significant after transplantation with patients who were upgraded to very good partial response or CR (early autologous HCT, 77% vs late autologous HCT, 56%, p<0.007). No significant differences were observed between groups for progression-free survival (PFS) or overall survival (OS), which were assessed at 1, 3, and 5 years; however, a difference of 10 months between groups in median PFS was noted (28 months for early autologous HCT patients vs 18 months for late autologous HCT patients). Relapse occurred in 40% of patients in the early autologous HCT group, and 55% of the late autologous HCT group (p=0.55). A variable that did have a significant bearing on PFS between groups was that of risk, with high-risk patients in the early autologous HCT group achieving a median PFS of 25 months, compared with the 11 months achieved by their counterparts in the late autologous HCT group. The results of this study seemed to confirm the observation made by previous studies that patients who achieve a CR are more likely to remain progression-free for significantly longer than those whose response to induction therapy is not very good. Data were lacking on the reason for delayed autologous HCT; another limitation was that patients who received maintenance therapy were excluded from the study.
Autologous HCT vs Standard Chemotherapy

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: is autologous HCT as initial treatment associated with improved health outcomes for patients with newly diagnosed MM?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The therapy being considered is autologous HCT as initial treatment.

Comparators
Comparators of interest include conventional chemotherapy with or without novel therapies.

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

Timing
Follow-up over months to years is of interest for relevant outcomes.

Setting
Patients are actively managed by hematologists and oncologists in an inpatient and outpatient clinical setting.

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

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

d. Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

One 2015, RCT compared autologous HCT with standard chemotherapy plus lenalidomide, a newer agent for treatment of MM. The open-label RCT from 59 centers in Europe and Australia used a 2×2 factorial design to compare 4 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 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% confidence interval [CI], 33.2 to 52.2 months) compared with chemotherapy plus lenalidomide (28.6 months; 95% CI, 20.6 to 36.7 months; p<0.0001). The rate of grade 3 or 4 adverse events was higher in the HCT groups than in the chemotherapy groups (hematologic events, 84% vs 26%; gastrointestinal complications, 20% vs 5%; infections, 19% vs 5%; all respectively).
Based on several prospective, randomized trials comparing conventional chemotherapy with high-dose therapy plus autologous HCT for patients with MM, autologous HCT has become the treatment of choice in patients younger than 65 years of age.

Data from seven randomized studies are available. In all but one (Barlogie et al [2006]), the CR rate was superior in the high-dose chemotherapy plus autologous HCT arm. The Barlogie et al (2006) study published final results from the phase 3 S9321 trial, which was initiated in 1993 and randomized 516 patients with MM to standard therapy or myeloablative conditioning with melphalan 140 mg/m² plus total body irradiation (TBI) followed by autologous HCT. These trialists reported virtually no difference in outcomes, including response rates, PFS, and OS. In five of the seven studies, the superior CR rate translated into significant increases in PFS. However, in the two 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. Three of the seven studies showed superior OS in the autologous HCT group.

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. The group that underwent autologous HCT had significantly improved response rates, event-free survival (EFS), and OS. Seven years later, the British Medical Research Council published similar results.

Systematic Reviews
A systematic review by Koreth et al (2007) of 2411 patients enrolled in RCTs compared standard-dose chemotherapy with myeloablative chemotherapy plus single autologous HCT. Meta-analysis concluded that myeloablative therapy with autologous HCT increased the likelihood of PFS (hazard ratio of progression, 0.75; 95% CI, 0.59 to 0.96) but not OS (hazard ratio of death, 0.92; 95% CI, 0.74 to 1.13); in this group, the odds ratio for treatment-related mortality (TRM) was 3.01 (95% CI, 1.64 to 5.50). However, the effects of myeloablative chemotherapy and autologous HCT might have been underestimated because up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HCT as salvage therapy when MM progressed. This could account for the lack of a significant difference in OS between the two groups.

Subsection Summary: Autologous HCT vs Standard Chemotherapy
For individuals with newly diagnosed MM, evidence from multiple RCTs have suggested that high-dose chemotherapy with autologous HCT is superior to standard chemotherapy in PFS, and possibly OS.

Tandem 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.

Tandem Autologous HCT
Clinical Context and Therapy Purpose
The purpose of tandem autologous HCTs is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with newly diagnosed MM.

The question addressed in this evidence review is: is tandem autologous HCT associated with improved health outcomes for patients with newly diagnosed MM?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest are individuals with newly diagnosed MM.

Interventions
The therapy being considered is tandem autologous HCT.

Comparators
Comparators of interest include conventional chemotherapy with or without novel therapies.

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

Timing
Follow-up over months to years is of interest for tandem autologous HCT to monitor relevant outcomes.

Setting
Patients are actively managed by hematologists and oncologists in an inpatient and outpatient clinical setting.

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

The first randomized trial of tandem autologous transplants (IFM-94) was published by Attal et al (2003). This trial randomized patients with newly diagnosed myeloma with single or tandem autologous transplants. Outcomes were analyzed by intention to treat (ITT) at 75-month follow-up. Among those randomized to single transplants (n=199), 148 relapsed. 33 were salvaged with a second autotransplant, 13 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Among those randomized to tandem autotransplants (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 EFS (20% vs 10% p=0.03), relapse-free survival (23% vs 13% p<0.01), and OS (42% vs 21% p=0.010), all respectively. TRM rates were 6% and 4% after tandem and single transplants, respectively (p=0.40). Second transplants extended survival only for those who failed to achieve a CR or without a very good partial response after 1 transplant (OS at 7 years, 43% vs 11%, respectively; p<0.001).

An accompanying editorial by Stadtmauer (2003) raised concerns that IFM-94 results might be specific to the regimen used for myeloablative therapy. Patients in the single transplant arm received melphalan 140 mg/m² plus 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 cited the IFM-95 study as evidence, suggesting melphalan 140 mg/m² plus TBI may be less effective and more toxic than myeloablative therapy plus melphalan 200 mg/m² and no TBI. Based on this, Stadtmauer (2003) hypothesized that increased survival in the IFM-94 tandem arm might have resulted from greater cumulative exposure to melphalan (280 mg/m² vs 140 mg/m²).

The Bologna 96 clinical study (2007) assessed single and double autologous HCT (n=321). 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=0.008), to prolong relapse-free survival (median, 42 months vs 24 months; p<0.001), and extend EFS (median, 35 months vs 23 months; p=0.001), all respectively. There was no significant difference between groups in TRM (3%-4%). There was a trend for improved OS among patients in the double transplant group (7-year rate, 60%) compared with the single transplant group (7-year rate, 47% p=0.10). Conversely, among patients achieving CR or near CR after one transplant, EFS and OS estimates did not differ significantly according to transplant(s) received by study randomization. A
Maffini et al (2018) published long-term follow-up results for multiple myeloma patients treated with tandem autologous-allogeneic HCT. 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: 48-60%) and 31% (95% CI: 25-36%), respectively; 10-year OS and PFS were 41% (95% CI: 34-48%) and 19% (95% CI: 13-24%), respectively. Overall non-relapse mortality was 2% at 100 days and 14% at 5 years. 34

Subsection Summary: Tandem Autologous HCT
Compared with single autologous HCT, a number of RCTs have demonstrated tandem autologous RCTs improved OS and recurrence-free survival in newly diagnosed MM.

Tandem Autologous HCT Followed by RIC Allo-HCT
Several trials have evaluated RIC allo-HCT following single or tandem autologous HCT. These trials were based on genetic randomization (i.e., patients with a human leukocyte antigen [HLA] identical sibling who were offered RIC allo-HCT following the autologous HCT), whereas the other patients underwent either single or tandem autologous transplants.

The first published, by Garban et al (2006), included high-risk patients.35, 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 ITT analysis, there was better median EFS and OS in the tandem autologous HCT group than in the RIC allo-HCT group (35 months vs 31.7 months, p=NS; 47.2 months vs 35 months, p=0.07, respectively). If results for only those patients who received autologous HTC followed by RIC allo-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=0.07). Updated results from this population were reported by Moreau et al (2008).36 Comparing the results of the 166 patients who completed the whole tandem autologous HCT protocol with 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=0.88), with a trend toward superior median OS in favor of double autologous HCT (57 months vs 41 months, respectively; p=0.08), due to 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).37 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=0.004). EFS and OS were superior for patients who underwent autologous plus allogeneic transplantation than for the tandem autologous transplantation (35 months vs 29 months; p=0.02; 80 months vs 54 months; p=0.01, respectively). Comparing the group who had HLA-identical siblings with those without, in a pseudo-ITT analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The TRM 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 graft-versus-host disease (GVHD).

Rosinol et al (2008) reported on the results of a prospective study of 110 patients with MM who failed to achieve at least near CR 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.38 The autologous followed by RIC allogeneic group had a higher CR rate (40% vs 11%, respectively; p=0.001) and a trend toward a longer median
PFS (31 months vs not reached, respectively; p=0.08). There were no statistical differences in EFS or OS estimates between groups. The autologous followed by RIC allogeneic group experienced a higher TRM rate (16% vs 5%, respectively; p=0.07) and had a 66% chance of chronic GVHD.

Although results differed between the Garban et al (2006) and the Moreau et al (2008) studies35,36 and the Bruno et al (2007) and the Rosinol et al (2008) studies37,38; these differences might have been due to study designs. The Moreau et al (2008) study focused on patients with high-risk disease and involved a conditioning regimen before the RIC allogeneic transplant that might have eliminated some of the graft-versus-myeloma effects. Other contributing factors might have been nonuniform preparative regimens, different patient characteristics, and criteria for advancing to a second transplant (i.e., 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 et al (2008) study. Reviewers suggested that the subgroup of high-risk patients with de novo MM might have had equivalent or superior results with a tandem autologous HCT vs a tandem autologous plus RIC allo-HCT and that, in patients with standard-risk and/or chemosensitive MM, RIC allograft might be an option.

Interim meeting abstracts for two prospective phase 3 trials comparing double autologous with single autologous followed by RIC allogeneic transplant have been published.39,40 At 36-month follow-up, the HOVON Group study (2008) found no significant differences between groups that received autologous followed by RIC allogeneic transplants and tandem autologous transplants in median EFS (34 months and 28 months, respectively) or in OS (80% and 75%, respectively).39 The other interim analysis of a European Group for Blood and Marrow Transplant (EBMT) study (2008) presented different inclusion criteria.40 Previously untreated patients received vincristine, doxorubicin, and dexamethasone or vincristine, doxorubicin, and dexamethasone-like induction treatment, and had a response status of at least stable disease (i.e., 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 cell transplant (if treated with 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 allo-HCT group and 248 to the autologous transplant group. Of patients allocated to the allogeneic group, 98 received a RIC allogeneic transplant. At interim reporting, no significant differences in PFS or OS estimates were noted between groups.

At 96 months in the EBMT trial (2013), PFS and OS rates were 22% and 49% vs 12% (p=0.027) and 36% (p=0.030) for tandem autologous plus RIC allo-HCT vs autologous HCT, respectively.41 The corresponding relapse or progression rates were 60% and 82% (p<0.001), respectively. Non-relapse mortality (NRM) rates at 36 months were 13% and 3% (p<0.001), respectively. In patients with the chromosome 13 deletion (del[13]), corresponding PFS and OS estimates were 21% and 5% (p=0.026) and 47% and 31% (p=0.154), respectively.41 Long-term outcomes in patients with MM were better with autologous HCT followed by RIC allo-HCT than with autologous HCT only, and the autologous followed by RIC allogeneic approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation.

Krishnan et al (2011) conducted a phase 3 trial comparing tandem autologous HCT with tandem autologous HCT plus RIC allo-HCT (tandem auto-allo group) in patients from 37 transplant centers in the United States, who, between 2003 and 2007, had received an autologous HCT (n=710).42 Of these patients, 625 had the 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 3 cycles of systemic therapy for myeloma within the past 10 months. Patients were assigned to a second autologous or allo-HCT based on the availability of an HLA-matched sibling donor. Patients in the tandem autologous group, 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% (42% to 51%) in the tandem autologous group (p=0.67). OS rates also did not differ at 3 years (77% [95% CI, 72% to 84%] vs 80% [CI, 77% to 84%]; p=0.19). Grade 3, 4, or 5 morbidity rates between the 2 groups were 46% and 42%, respectively. The data suggested nonmyeloablative tandem auto-allo-HCT was no more effective than tandem autologous HCT for patients with standard-risk myeloma.

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

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

The question addressed in this evidence review is: is allo-HCT associated with improved health outcomes for patients with newly diagnosed MM?

The following PICOTS were used to select literature to inform this review.

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

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

Comparators
Comparators of interest include conventional chemotherapy with or without novel therapies.

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

Timing
Follow-up over months to years is of interest for relevant outcomes.

Setting
Patients are actively managed by hematologists and oncologists in an inpatient and outpatient clinical setting.

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

Although myeloablative allo-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.

In an approach to reduce NRM associated with allo-HCT, RIC methods have been investigated. Most studies are phase 2, with no comparison with other treatment modalities. One retrospective study has compared myeloablative with nonmyeloablative conditioning. This study, conducted by the EBMT, found that TRM was significantly reduced with RIC but, because of a higher relapse or progression rate, there was no significant improvement in OS.

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

**Section Summary: Allo-HCT**

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.\textsuperscript{46,47} The evidence for allo-HCT is insufficient to draw conclusions.

**Relapsed or Refractory MM**

**Salvage Autologous HCT**

**Clinical Context and Therapy Purpose**

The purpose of autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with relapsed MM after failing an autologous HCT.

The question addressed in this evidence review is: is autologous HCT associated with improved health outcomes for patients with relapsed MM after failing an autologous HCT?

The following PICOTS were used to select literature to inform this review.

**Patients**

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

**Interventions**

The therapy being considered is autologous HCT.

**Comparators**

Comparators of interest include conventional chemotherapy with or without novel therapies.

**Outcomes**

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

**Timing**

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

**Setting**

Patients are actively managed by hematologists and oncologists in an inpatient and outpatient clinical setting.

**Study Selection Criteria**

Methodologically credible studies were selected using principles detailed above.

Despite improved survival rates with autologous HCT vs conventional chemotherapy, many patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HCT include biologic agents (e.g., thalidomide, lenalidomide, bortezomib, as single agents, or in combination with dexamethasone, or in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HCT.\textsuperscript{48}

The Myeloma X Relapse trial was a multicenter, randomized, open-label, phase 3 study involving 51 centers across the United Kingdom, with enrollment occurring between 2008 and 2012. Inclusion criteria were patients at least 18 years and with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT (NCT00747877; EudraCT 2006-005890-24).\textsuperscript{49} Before randomization, eligible patients received
bortezomib, doxorubicin, and dexamethasone (PAD) 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/m² plus salvage autologous HCT or to oral cyclophosphamide 400 mg/m²/wk for 12 weeks. The primary endpoint was time to disease progression, analyzed by ITT. A total of 297 patients were enrolled, of whom 293 received PAD reinduction 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; HR=0.36; 95% CI, 0.25 to 0.53; p<0.001). Frequently reported (>10% of patients) grade 3 or 4 adverse events with PAD induction, salvage HCT, and cyclophosphamide were: neutropenia (43% [125/293] patients receiving PAD vs 76% [63/83] patients receiving salvage HCT vs 13% [11/84] patients receiving cyclophosphamide), thrombocytopenia (51% [150] after PAD, 72% [60] vs 5% [4]), and peripheral neuropathy (12% [35] after PAD, and none vs none), all respectively.

Final survival data for the Myeloma X Relapse trial were reported in 2016.50 The HCT group had a superior median OS (67 months; 95% CI, 55 months to not estimable) compared with the chemotherapy group (52 months; 95% CI, 42 to 60 months; p<0.001). 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=0.02). 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% to 8.2%).

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.51 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 the 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=0.026). 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.

A review by Zogas 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, 85-40 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.

Tandem Autologous HCT for Relapse After First Autologous HCT

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: is tandem HCT associated with improved health outcomes for patients with refractory MM after failing a first HCT?

The following PICOTS were used to select literature to inform this review.

Patients

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

Comparators of interest include conventional chemotherapy with or without novel therapies.

Outcomes

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

Timing

Follow-up over months to years is of interest for tandem autologous HCT to monitor relevant outcomes.

Setting

Patients are actively managed by hematologists and oncologists in an inpatient and outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using principles detailed above.

A 2003 evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation summarized data from 4 relevant clinical series. Reviews reported that some myeloma patients who relapsed after a first autotransplant achieved durable complete or partial remissions after a second autotransplant as salvage therapy. Factors found to increase the likelihood of durable remissions and extend survival included a chemosensitive relapse, younger age, long disease-free or progression-free interval since the initial autotransplant, and fewer chemotherapy regimens before the initial autotransplant. Olin et al (2009) reported their experience with 41 patients with MM who received a second salvage autologous HCT for relapsed disease. The median time between transplants was 37 months (range, 3-91 months). The overall response rate in assessable patients was 55%. TRM was 7%. Median follow-up was 15 months, with median PFS of 8.5 months and median OS 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.
A review by McCarthy and Holstein (2016) summarized current treatment regimens for patients with myeloma who are eligible for autologous HCT or allo-HCT.54, 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 2 studies showing a benefit in patients given autologous HCT following relapse (hazard ratio, 0.57; p=0.037). 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.

**Section Summary: Relapsed or Refractory MM**

Autologous HCT in patients relapsed MM have shown improved PFS and OS rates compared with conventional chemotherapy.

**Allo-HCT for Relapse After Initial Autologous HCT**

Qazilbash et al (2006) reported their experience with salvage autologous HCT or allo-HCT after a failed first autologous transplant.55, 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 transplant was 25 months for the autologous group and 17 months for the allogeneic group. After a median follow-up of 18 months (range, 2-69 months) for the autologous group, median PFS was 6.8 months, and OS was 29 months. After a median follow-up of 30 months (range, 13-66 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 one year between the first and salvage transplants predicted a significantly better OS (p=0.02). 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).

The EBMT (2013) analyzed 413 MM patients who received a related or unrelated RIC allo-HCT for the treatment of relapse or disease progression after a prior autologous HCT.56, Median age at RIC allo-HCT was 54 years, and 45% of patients had undergone 2 or more prior autologous transplants. Median OS and PFS from the time of allogeneic transplantation for the entire population were about 25 months and 10 months, respectively. Cumulative NRM at 1 year was about 22%. In a multivariate analysis, cytomegalovirus seronegativity of both patient and donor was associated with significantly better PFS, OS, and NRM. Patient-donor sex mismatch was associated with better PFS; fewer than two prior autologous transplants were associated with better OS, and a shorter time from the first autologous HCT to the RIC allo-HCT was associated with lower NRM. These results suggested patient and donor cytomegalovirus seronegativity represent key prognostic factors for outcome after RIC allo-HCT for MM that relapses or progresses following one or more autologous transplants.

Schneidawind et al (2017) retrospectively analyzed data from 41 myeloma patients who were treated with allogeneic stem cell transplantation for relapsed or refractory disease between 2001 and 2015.57 Among various immunosuppression regimens, anti-thymocyte globulin was given to 35 (85%) of the patients; conditioning regimens were myeloablative in 15 patients, reduced-intensity myeloablative in 18 patients, and nonmyeloablative in 8 patients. In univariate analysis, EFS was significantly lower for the 18 patients who received a tandem autologous HCT prior to the allo-HCT than for the 23 patients who received either a single autologous HCT or no transplant before the current treatment (6% vs 24%, respectively; hazard ratio, 0.48; 95% CI, 0.23 to 0.98; p=0.04). At the latest follow-up, a total of 25 patients had died, 14 (56%) of whom died of relapse or refractory disease. Salvage regimens (thalidomide, lenalidomide, pomalidomide,
bortezomib, or a combination) were given to 20 patients, who showed significantly improved OS rates at 1 year (79%) and 3 years (68%), compared with the rest of the cohort (1-year OS=29%, p=0.001; 3-year OS=14%, p=0.004).

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.58 Among the treatments suggested were immunomodulatory drugs (i.e., thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (i.e., bortezomib, carfilzomib, ixazomib), monoclonal antibodies, and autologous HCT and allo-HCT. Reviewers noted that most of the studies of stem cell transplantation 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.

**POEMS Syndrome**

**Clinical Context and Therapy Purpose**

The purpose of HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with POEMS syndrome.

The question addressed in this evidence review is: is HCT associated with improved health outcomes for patients with POEMS syndrome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with POEMS syndrome.

**Interventions**
The therapy being considered is HCT.

**Comparators**
Comparators of interest include conventional chemotherapy with or without novel therapies.

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

**Timing**
Follow-up over months to years is of interest for HCT to monitor relevant outcomes.

**Setting**
Patients are actively managed by hematologists and oncologists in an inpatient and outpatient clinical setting.

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

**Systematic Reviews**
A 2012 Cochrane review has provided a comprehensive source on the treatment of POEMS syndrome.11 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. 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/m².5 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.

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.59 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 rate of 94% and a PFS rate of 75% among 59 patients entered between 1999 and late 2011.60 A second series (2014) included 9 patients with advanced POEMS syndrome who had Eastern Cooperative Oncology Group Performance Status scores of 3 or 4 and were treated with high-dose melphalan therapy followed by autologous HCT from 2004 to 2011.61 Eight patients achieved an initial hematologic response, four of whom had CRs. At a median follow-up of 44 months (range, 8-94 months), 7 patients were alive, with a 3-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.62 Engraftment was successful in most patients (96.8%); engraftment syndrome (n=29; 23%) did not appear significantly associated either with previous treatment (p=0.018) or the inclusion of cyclophosphamide as a mobilizer (p=0.590). Following transplantation, 48% of patients had achieved hematologic CR (n=49), 16 of whom were in a lower status preceding autologous HCT. At the 3-year follow-up, the likelihood of relapse was 12% (95% CI, 5% to 18%); after 5 years, the likelihood of PFS was 74% (95% CI, 63.2% to 83.7%). Rates of NRM and OS after 5 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=0.032), 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 of HCT for POEMS syndrome, but cohort studies and case series have reported improvements 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 MM
For individuals who have newly diagnosed MM who receive autologous HCT as initial treatment, the evidence includes several prospective, RCTs that compared conventional chemotherapy with high-dose chemotherapy plus autologous HCT. The relevant outcomes include OS and treatment-related morbidity. In general, the evidence has suggested OS 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. 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. The relevant outcomes include OS and treatment-related morbidity. Compared with single autologous HCT, a number of RCTs have demonstrated tandem autologous HCT improves OS and recurrence-free survival in newly diagnosed MM. The available RCTs compare RIC allo-HCT following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on genetic randomization (i.e., patients with a human leukocyte antigen-identical sibling who were offered RIC allo-HCT following autologous HCT), whereas other patients underwent either one or two autologous transplants. Although the body of evidence has shown inconsistencies regarding OS and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allo-HCT, although at the 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 with as initial or salvage treatment, the evidence includes nonrandomized studies. The relevant outcomes include OS and treatment-related morbidity. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Relapsed or Refractory MM
For individuals who have relapsed MM after failing an autologous HCT who receive autologous HCT, the evidence includes an RCT, a retrospective study, a systematic review summarizing data from four series of patients who relapsed after a first autologous HCT, and a review summarizing recent studies on a second autologous HCT in relapsed myeloma. The relevant outcomes include OS 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 OS rates are improved with autologous HCT compared with conventional chemotherapy 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 three RCTs and a review. The relevant outcomes include OS and treatment-related morbidity. The evidence has shown tandem autologous HCT improves OS rates in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
POEMS Syndrome
For individuals who have POEMS syndrome who receive HCT, the evidence includes case reports and series. The relevant outcomes include OS 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 concerning treatment approaches and peritransplant support. However, for patients with disseminated POEMS syndrome, a chain of evidence and contextual factors related to the disease and MM would suggest improvement in health outcomes with autologous HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information
Clinical Input 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 from Blue Cross Blue Shield Association, input was received from 1 specialty medical society, 1 academic medical center, and 2 Blue Distinction Centers for Transplant in 2017. There was a consensus that allogeneic hematopoietic cell transplantation (HCT) is investigational for newly diagnosed multiple myeloma and as salvage therapy after primary graft failure and for the primary progressive disease.

2013 Input
In response to requests from Blue Cross Blue Shield Association, input was received from 3 academic medical centers and 6 Blue Distinction Centers for Transplant in 2013. There was near-consensus that autologous HCT is medically necessary for POEMS syndrome and near-consensus that allogeneic and tandem HCT are investigational for POEMS syndrome.

2010 Input
In response to requests from Blue Cross Blue Shield Association, input was received from 2 academic medical centers in 2010. One reviewer agreed with the current policy statement related to tandem autologous HCT followed by reduced-intensity conditioning allogeneic HCT and the other disagreed. Those providing input agreed with the other policy statements. (The conclusion that allogeneic HCT is investigational for salvage therapy was a late addition to the policy and was not sent for clinical input.)

Practice Guidelines and Position Statements
American Society for Blood and Marrow Transplantation
The ASBMT (2015) published evidence-based guidelines on the use of HCT in patients with multiple myeloma (MM). 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. ASBMT guidelines did not address POEMS or other plasma cell dyscrasias besides MM.

The ASBMT, and 3 other groups (2015) published joint guidelines based on an expert consensus conference. These guidelines contained the following recommendations for HCT as salvage therapy:

"...autologous HCT: (1) In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with HCT as part of salvage therapy should be considered standard; (2) 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; (3) High-dose therapy and autologous HCT can be used as bridging strategy to allogeneic HCT; (4) 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, -modulating agents, and oral proteasome inhibitors; (5) 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 remissions) after primary therapy and (6) Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM [multiple myeloma] relapsing after primary therapy comparing to ‘best non-HCT’ therapy.

Regarding allogeneic HCT...: (1) 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 and/or with high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Allogeneic HCT should be performed in the context of a clinical trial if possible; (3) The role of post allogeneic HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.”

International Myeloma Working Group
The 2010 conclusions and recommendations of the International Myeloma Working Group consensus statement on the current status of allogeneic HCT (allo-HCT) for MM are as follows: Myeloablative allo-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. Nonmyeloablative allo-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 compared with autologous HCT.

National Comprehensive Cancer Network
Autologous HCT
The NCCN guidelines (v.3.2018) consider autologous HCT a category 1 recommendation as a follow-up to induction therapy for newly diagnosed MM and as a category 1 recommendation for relapsed or progressive disease if the patient is considered a transplant candidate.

Tandem HCT
The NCCN recommends collecting enough stem cells for two transplants in all eligible patients.

Allo-HCT
The NCCN recommends the following for allo-HCT: “Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably on a clinical trial. Current data do not support miniallografting alone” (category 2A).

POEMS Syndrome
The NCCN guidelines do not address the treatment of POEMS syndrome.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Medicare has the following national coverage determination for the use of HCT for MM. "Effective ... January ... 2016, allogeneic HSCT [hematopoietic stem cell transplantation] for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma and..."
participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

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

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
- (optional) Quality of life?"

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
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<tr>
<td>NCT01208662</td>
<td>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</td>
<td>660</td>
<td>Sep 2018</td>
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<tr>
<td>NCT02322320</td>
<td>Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 (BMT CTN #Q07LT)</td>
<td>450</td>
<td>Dec 2018</td>
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<tr>
<td>NCT00177047</td>
<td>Autologous Transplantation for Multiple Myeloma</td>
<td>363</td>
<td>Jan 2020</td>
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<tr>
<td>NCT01109004</td>
<td>A Trial of Single Autologous Transplant With or Without Consolidation Therapy Versus Tandem Autologous Transplant With Lenalidomide Maintenance for Patients With Multiple Myeloma (BMT CTN 0702)</td>
<td>750</td>
<td>Mar 2018</td>
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<tr>
<td>NCT01191060</td>
<td>Randomized Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone to High-Dose Treatment With ASCT in the Initial Management of Myeloma in Patients up to 65 Years of Age</td>
<td>700</td>
<td>Sep 2020</td>
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<tr>
<td>NCT01208766</td>
<td>A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone (VMP) With High Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma</td>
<td>1500</td>
<td>Apr 2021</td>
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<tr>
<td>Unpublished</td>
<td></td>
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<tr>
<td>NCT00998270</td>
<td>Autologous Bone Marrow Transplantation (BMT) Compared With Allogeneic BMT in Multiple Myeloma</td>
<td>185</td>
<td>Oct 2017 (unknown)</td>
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</tbody>
</table>

NCT: national clinical trial.

References


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
• Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient’s ability to be an adequate candidate for transplant
• Radiology reports including:
  o Chest x-ray (CXR)
  o PET scan, CT scan and bone survey (as appropriate)
• Cardiology procedures and pulmonary function reports:
  o EKG
  o Echocardiogram
  o Pulmonary function tests (PFTs)
• Biopsy/Pathology reports including:
  o Bone marrow biopsy
  o Lymph node biopsy (as appropriate)
• Laboratory reports

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<thead>
<tr>
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<th>Code</th>
<th>Description</th>
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<td></td>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
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<td></td>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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<tr>
<td></td>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
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<td></td>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
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<td></td>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest; T-cell depletion</td>
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<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
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<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
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<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
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<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
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<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
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<tr>
<td></td>
<td>38220</td>
<td>Diagnostic bone marrow; aspiration(s)</td>
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<tr>
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<td>38222</td>
<td>Diagnostic bone marrow; biopsy(ies) and aspiration(s)</td>
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<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
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<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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**HCPCS**

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<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
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<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition</td>
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**ICD-10 Procedure**

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<td>Transfusion of Allogeneic Related Bone Marrow into Central Vein, Percutaneous Approach</td>
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<tr>
<td>30243G3</td>
<td>Transfusion of Allogeneic Unrelated Bone Marrow into Central Vein, Percutaneous Approach</td>
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<td>30243G4</td>
<td>Transfusion of Allogeneic Unspecified Bone Marrow into Central Vein, Percutaneous Approach</td>
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<td>30243X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
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<td>Transfusion of Allogeneic Related Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
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<tr>
<td>30243X3</td>
<td>Transfusion of Allogeneic Unrelated Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
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<td>30243X4</td>
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<tr>
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<tr>
<td>30243Y2</td>
<td>Transfusion of Allogeneic Related Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
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<td>30243Y3</td>
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<td>30243Y4</td>
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<td>30250G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Peripheral Artery, Open Approach</td>
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<tr>
<td>30250X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Artery, Open Approach</td>
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<tr>
<td>30250Y0</td>
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<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Artery, Open Approach</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<tr>
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<td>BCBSA Medical Policy adoption</td>
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<td>03/30/2015</td>
<td>Policy revision without position change</td>
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<td>03/01/2017</td>
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<td>topoietic Stem-Cell Transferable for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome</td>
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<td>01/01/2018</td>
<td>Coding update</td>
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Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions,
but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.