I. Policy

Multiple myeloma

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

Tandem autologous-autologous hematopoietic stem-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.)

Tandem transplantation with an initial round of autologous hematopoietic stem-cell transplantation (SCT) 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 stem-cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

POEMS syndrome

Autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome. (See Policy Guidelines)

Allogeneic and tandem hematopoietic stem-cell transplantation are considered investigational to treat POEMS syndrome. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure for these indications.
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 MM 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.

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

Cross-references:

MP-9.038 Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
MP-9.039 Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
MP-9.040 Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
MP-9.041 Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia
MP-9.042 Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
MP-9.043 Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
MP-9.045 Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
MP-9.046 Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia
MP-9.047 Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer
MP-9048 Hematopoietic Stem-Cell Transplantation Miscellaneous Solid Tumors in Adults
MP-9.049 Hematopoietic Stem-Cell Transplantation for Breast Cancer
MP-9.050 Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma
MP-9.052 Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors
MP-9.053 Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
MP-9.054 Hematopoietic Stem-Cell Transplantation for Solid Tumors of Children
MP-9.055 Allogeneic HSCT for Genetic Diseases and Acquired Anemias
MP-9.056 Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.
III. DESCRIPTION/BACKGROUND

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to 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 radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). 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 “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in MP-9.001.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Conventional Preparative Conditioning for HSCT

The conventional (“classical”) practice of allogeneic HSCT 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 pretransplant...
Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less-intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also 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. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT 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 the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

Multiple Myeloma

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 the time of diagnosis, most patients have generalized disease, and, the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease. 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. Multiple myeloma usually evolves from an asymptomatic premalignant stage (termed “monoclonal gammopathy of undetermined significance” or MGUS). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic multiple myeloma prolongs survival when compared to therapy delivered at the time of symptoms or end-organ damage. (2,3) In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized and referred to as smoldering multiple myeloma. The overall risk of disease progression from smoldering to symptomatic multiple myeloma is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 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 suggests it is mediated by 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 1 of the minor criteria are necessary for diagnosis.7

**Table 1: Criteria and Associations**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Known Associations</th>
<th>Possible Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Monoclonal plasma-proliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td></td>
<td>Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)</td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
</tr>
<tr>
<td></td>
<td>Edema (edema, pleural effusion, ascites)</td>
<td>Polycythemia</td>
<td>Arthralgias</td>
</tr>
<tr>
<td></td>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangioma, white nails)</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Papilledema</td>
<td>Low vitamin B_{12} values</td>
<td>Diarrhea</td>
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The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.8 Other large series have been described in the United States5,7,9 and in India.10 In general, patients with POEMS have a superior OS compared with that of MM, nearly 14 years in a large series from Mayo Clinic.7 However, given the rarity of POEMS, no randomized controlled trials (RCTs) of therapies have been reported.11 Numerous approaches
have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HSCT support. Optimal treatment involves eliminating the plasma cell clone, for example, by surgical excision or local radiotherapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.

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, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

IV. RATIONALE

MM Treatment Overview
In the prechemotherapy era, the median survival for a patient diagnosed with MM was approximately 7 months. After the introduction of chemotherapy (eg, 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 (OS) reported during a 24-year period from 1971-1994, with a trend toward improvement during 1995-2000 and a statistically significant benefit in OS during 2001-2006. These data suggested that autologous stem cell transplantation (SCT) 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/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 have responsive disease with initial therapy, and only a small minority will have refractory disease.

Risk-Adapted Therapy
The approach to the treatment of newly diagnosed MM (symptomatic) is dictated by eligibility for autologous hematopoietic stem cell transplantation (HSCT) and risk-stratification. Risk stratification, using fluorescent in situ hybridization and conventional karyotyping divides patients into standard- or high-risk categories.
High-risk patients, which comprise approximately 25% of patients with MM, are defined by any of the following cytogenetic findings: 17p deletion, t(4;14), t(14;16), t(14;20), deletion 13 or hypodiploidy.\textsuperscript{18} Standard-risk patients are those with hyperdiploidy, t(11;14) or t(6;14).

Standard-risk patients are typically treated with non-alkylator-based therapy such as lenalidomide plus low-dose dexamethasone followed by autologous HSCT; 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. High-risk patients are generally treated with a bortezomib-based induction followed by autologous HSCT and then bortezomib-based maintenance.\textsuperscript{18}

Recent reviews highlight the treatment of newly diagnosed myeloma,\textsuperscript{19} relapsed, and refractory myeloma.\textsuperscript{20} A review of the literature highlights advances in the use of autologous and allogeneic HSCT.\textsuperscript{21}

**Single Autologous HSCT Versus Standard Chemotherapy**

As a result of several prospective, randomized trials that were conducted comparing conventional chemotherapy with high-dose therapy and autologous HSCT for patients with MM, autologous HSCT has become the treatment of choice in patients younger than 65 years of age.

Data from 7 randomized studies are available.\textsuperscript{22-28} In all but 1 study,\textsuperscript{24} the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HSCT arm: this study published final results of the S9321 trial, which was initiated in 1993 and randomized 516 patients with MM to receive either standard therapy or myeloablative conditioning with melphalan 140 mg/m\textsuperscript{2} plus total body irradiation followed by autologous HSCT.\textsuperscript{24} The authors reported virtually no difference in outcomes, including response rates, progression-free survival (PFS), and OS.

In 5 of the 7 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 HSCT, randomization was not performed at diagnosis but only after induction treatment, possibly introducing selection bias.\textsuperscript{22} Three of the 7 studies showed superior OS in the autologous HSCT group.\textsuperscript{23,26,28}

The Intergroupe Francophone du Myélome (IFM) showed the superiority of high-dose chemotherapy and autologous HSCT compared with conventional chemotherapy in a randomized trial of 200 patients younger than 65 years of age.\textsuperscript{23} The group that underwent autologous HSCT had significantly improved response rates, event-free (EFS), and OS. Seven years later, the British Medical Research Council published similar results.\textsuperscript{26}

The reasons for the discrepant results among these randomized studies are uncertain but may be related to the conditioning regimens or patient age.

A meta-analysis of 2411 patients enrolled in randomized controlled trials (RCTs) compared standard-dose chemotherapy versus myeloablative chemotherapy with single autologous HSCT.\textsuperscript{29} The authors of the meta-analysis concluded that myeloablative therapy with autologous HSCT increased the likelihood of PFS (hazard of progression, 0.75; 95% confidence interval}
[CI], 0.59 to 0.96) but not OS (hazard of death, 0.92; 95% CI, 0.74 to 1.13); the odds ratio for treatment-related mortality (TRM) was 3.01 (95% CI, 1.64 to 5.50) in the group with autologous HSCT. However, the effects of myeloablative chemotherapy and autologous HSCT may have been diluted by the fact that up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HSCT as salvage therapy when the MM progressed. This could account for the lack of a significant difference in OS between the two groups in the study.

These randomized trials of autologous HSCT following induction therapy were designed and implemented before the availability of thalidomide, lenalidomide, and bortezomib. The introduction of these agents has dramatically changed the treatment paradigm of MM. Ongoing trials incorporating these newer agents into induction regimens are ongoing. Preliminary results have shown CRs in a substantial proportion of these patients, opening the question as to what role autologous HSCT will continue to play. However, it will require further follow-up to determine if these newer induction regimens will translate into improved survival.

30 **Salvage HSCT**

Despite the success in improved survival with autologous HSCT versus conventional chemotherapy, nearly all patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HSCT include novel biologic agents (eg, thalidomide, lenalidomide, bortezomib, as single agents, in combination with dexamethasone, and in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HSCT.

31 In a multicenter, randomized, open-label, phase 3 study from 51 centers across the United Kingdom, between April 16, 2008, and November 19, 2012, Cook et al recruited patients aged at least 18 years with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HSCT (NCT00747877) and EudraCT (2006-005890-24). 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 randomly assigned (1:1) to receive either high-dose melphalan 200 mg/m² plus salvage autologous HSCT or oral cyclophosphamide (400 mg/m²/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 PAD reinduction therapy. Among the latter, 174 patients with sufficient harvest of peripheral blood stem cells were randomly allocated to undergo salvage HSCT (n=89) or receive cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HSCT group than in the cyclophosphamide group (19 months [95% CI, 16 to 25] vs 11 months [95% CI, 9 to 12]; hazard ratio, 0.36 [95% CI, 0.25 to 0.53]; p<0.001). Frequently reported (>10% of patients) grade 3-4 morbidity with PAD induction, salvage HSCT, and cyclophosphamide were: neutropenia (125 [43%] of 293 patients after PAD and 63 [76%] of 83 patients in the salvage HSCT group vs 11 [13%] of 84 patients in the cyclophosphamide group), thrombocytopenia (150 [51%] after PAD, 60 [72%] vs 4 [5%], respectively), and peripheral
neuropathy (35 [12%] after PAD, and none vs none, respectively). This study provides additional
evidence for a net benefit of high-dose melphalan plus salvage HSCT when compared with
cyclophosphamide in patients with relapsed MM eligible for intensive therapy.

**Repeat Autologous HSCT for Relapse After Initial Autologous HSCT**
An evidence-based systematic review sponsored by the American Society for Blood and
Marrow Transplantation summarized data from 4 relevant clinical series. Investigators 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 that apparently
increased the likelihood of durable remissions and extended survival included a chemosensitive
relapse, younger age, a long disease-free or progression-free interval since the initial
autotransplant, and fewer chemotherapy regimens before the initial autotransplant. Thus, clinical
judgment plays an important role in selecting patients for this treatment with a reasonable
likelihood that potential benefits may exceed harms.

Olin et al reported their experience with 41 patients with MM who received a second salvage
autologous HSCT for relapsed disease. Median time between transplants was 37 months
(range, 3-91 months). Overall response rate in assessable patients was 55%. Treatment-related
mortality was 7%. Median follow-up time 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.

**Allogeneic HSCT for Relapse After Initial Autologous HSCT**
Qazilbash et al reported their experience with salvage autologous or allogeneic transplantation
after a failed first autologous transplant. Fourteen patients (median age, 52 years) received a
second autologous transplant, and 26 patients (median age, 51 years) underwent a reduced-
intensity allogeneic transplant. Median interval between first and second transplant was 25 and
17 months for the autologous and allogeneic groups, respectively. 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, respectively. 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. On univariate
analysis, in the allogeneic group, an interval of greater than 1 year between the first and salvage
transplants predicted a significantly better OS (p=0.02). None of the prognostic factors that were
evaluated for the allogeneic group was found to have a significant impact on survival in the
autologous group (which included age, cytogenetics, type of donor, and chronic graft-versus-host
disease [GVHD], among others).

European Group for Blood and Marrow Transplant (EBMT) reported an analysis of 413 MM
patients who received a related or unrelated reduced-intensity conditioning (RIC) allogeneic
HSCT for the treatment of relapse or disease progression after a prior autologous HSCT. Median age at RIC allogeneic HSCT was 54 years, and 45% of patients had undergone 2 or more
prior autologous transplants. The median OS and PFS from the time of allogeneic transplantation
for the entire population were about 25 and 10 months, respectively. Cumulative nonrelapse
mortality (NRM) at 1 year was about 22%. In a multivariate analysis, cytomegalovirus (CMV)
seronegativity of both patient and donor was associated with significantly better PFS, OS, and NRM. Patient-donor gender mismatch was associated with better PFS, fewer than 2 prior autologous transplants was associated with better OS, and shorter time from the first autologous HSCT to the RIC allogeneic HSCT was associated with lower NRM. These results suggest patient and donor CMV seronegativity represent key prognostic factors for outcome after RIC allogeneic HSCT for MM that relapses or progresses following 1 or more autologous transplants.

**Tandem HSCT**

A tandem transplant involves an autologous transplant followed by a preplanned second transplant, either another autologous or a 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-Autologous HSCT**

The first randomized trial of autologous tandem transplants (IFM-94) was published in December 2003 by Attal et al and randomized patients with newly diagnosed myeloma to single or tandem autologous transplants. Outcomes were analyzed by intention to treat at 75-month median 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%, respectively; p=0.03), relapse-free survival (RFS; 23% vs 13%, respectively; p<0.01), and OS (42% vs 21%, respectively; p=0.010). TRM was 6% and 4% after tandem and single transplants, respectively (p=0.40). Second transplants apparently extended survival only for those who failed to achieve a CR or very good partial response (VGPR) after 1 transplant (OS at 7 years, 43% vs 11%, respectively; p<0.001).

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

The Bologna 96 clinical study compared single with double autologous HSCT (n=321). Patients undergoing tandem autologous HSCT were more likely than those with a single autologous HSCT to attain at least a near CR (47% vs 33%, respectively; p=0.008), to prolong RFS (median, 42 vs 24 months, respectively; p<0.001), and extend EFS (median, 35 months vs
23 months, respectively; p=0.001). 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, 60%), compared with the single-transplantation group (7-year rate, 47%; p=0.10). Conversely, among patients achieving CR or near CR after 1 transplantation, EFS and OS were not significantly different according to transplantation(s) received by study randomization. A subgroup analysis of outcomes of patients assigned to the two treatment arms was evaluated according to response and showed that the benefit of a second transplant was particularly evident in patients who failed at least near CR the first autologous transplant.

Tandem Autologous-RIC Allogeneic HSCT

Several RCTs have been published comparing RIC-allogeneic HSCT following a first autologous HSCT with autologous transplants, single or in tandem. These studies were based on “genetic randomization,” that is, patients with an HLA-identical sibling were offered an RIC-allogeneic HSCT following the autologous HSCT, whereas the other patients underwent either 1 or 2 autologous transplants.

The first published study by Garban et al included high-risk patients (including deletion of chromosome 13). Sixty-five patients were in the autologous/RIC-allogeneic group and 219 in the autologous/autologous group. Based on the intention-to-treat analysis, there was better median EFS and OS in the autologous/autologous 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 actually received the autologous/RIC-allogeneic (n=46) or tandem autologous transplants (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 of this population were reported with a reference date of July 2008 by Moreau et al. Comparing the results of the 166 patients who completed the whole tandem autologous HSCT protocol to the 46 patients who underwent the entire autologous/RIC-allogeneic program, no difference was seen regarding EFS (median, 25 months vs 21 months, respectively; p=0.88), with a trend toward superior OS in favor of double autologous HSCT (median OS, 57 months vs 41 months, respectively; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

One study by Bruno et al included 80 patients with an HLA-identical sibling and who were allowed to choose allografts or autografts for the second transplant (58 completed an autograft/allograft sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence). The results among those completing tandem transplantation showed a higher CR rate at the completion of the second transplant for the autograft/allograft group (55%) than for the autograft/autograft group (26%; p=0.004). EFS and OS were superior for the patients who underwent autologous-allogeneic transplantation (35 months vs 29 months; p=0.02 and 80 months vs 54 months; p=0.01, respectively). Analyzing the group with HLA-identical siblings versus those without, in a pseudo intention-to-treat analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The TRM rate at 2 years was 2% in the double autograft group and 10% in the autograft/allograft group; 32% of the latter group had extensive, chronic GVHD.
Rosinol et al reported the results of a prospective study of 110 patients with MM who failed to achieve at least near CR after a first autologous HSCT 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. The autologous/RIC-allogeneic group had a higher CR rate (40% vs 11%, respectively; p=0.001) and a trend toward a longer PFS (median, 31 months vs not reached, respectively; p=0.08). There was no statistical difference in EFS or OS between the 2 groups. The autologous/RIC-allogeneic group experienced a higher transplantation-related mortality rate (16% vs 5%, respectively; p=0.07) and a 66% chance of chronic GVHD.

Although the results differ among the Garban/Moreau study and the other 2 studies, this may be due to different study designs. The Moreau et al 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 nonuniform 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 et al study. The authors suggest that the subgroup of high-risk patients with de novo MM may have equivalent or superior results with a tandem autologous/autologous transplant versus a tandem autologous/RIC-allogeneic transplant and that in patients with standard-risk and/or chemosensitive MM, RIC allograft may be an option.

Interim results of 2 prospective phase 3 trials that compared double autologous with single autologous followed by RIC-allogeneic transplant have been published. The HOVON Group study at 36 months of follow-up found no significant difference between the groups that received autologous/RIC-allogeneic transplants or tandem autologous transplants in EFS (median, 34 months and 28 months, respectively) or OS (80% and 75%, respectively) at 36 months.

An interim analysis of an EBMT study presented somewhat different inclusion criteria. 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-allogeneic transplantation, 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 transplant group and 248 to the autologous transplant group. Of the patients allocated to the allogeneic group, 98 received an RIC-allogeneic transplant. At interim publication, no significant difference in PFS or OS was noted between the double autologous and autologous/RIC-allogeneic transplant recipients.

At 96 months in the EBMT trial, PFS and OS were 22% and 49% versus 12% (p=0.027) and 36% (p=0.030) with autologous/RIC-allogeneic and autologous HSCT, respectively. The corresponding relapse/progression rate (RL) was 60% versus 82% (p<0.001). Nonrelapse
mortality at 36 months was 13% versus 3% (p<0.001). In patients with the del(13) abnormality, corresponding PFS and OS were 21% and 47% versus 5% (p=0.026), and 31% (p=0.154). Long-term outcome in patients with MM was better with autologous/RIC-allogeneic HSCT compared with autologous only, and the autologous/RIC-allogeneic approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation.

Krishnan et al conducted a phase 3 trial comparing tandem autologous-autologous HSCT (auto-auto group) versus tandem autologous-RIC allogeneic HSCT (auto-allo group) in patients from 37 transplant centers in the U.S., who between 2003 and 2007, had received an autologous HSCT (n=710). Of these patients, 625 had standard-risk disease, and 156 of 189 patients (83%) in the auto-allo group and 366 of 436 (84%) in the auto-auto group received a second transplant. Patients were eligible 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 receive a second autologous or allogeneic HSCT based on the availability of an HLA-matched sibling donor. Patients in the auto-auto group subsequently underwent random assignment 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 auto-allo group and 46% (42 to 51) in the auto-auto group (p=0.67). OS also did not differ at 3 years (77% [95%, CI, 72 to 84] vs 80% [CI, 77 to 84]; p=0.19). Grade 3-5 morbidity between the 2 groups were 46% and 42%, respectively. The data suggest nonmyeloablative allogeneic HSCT after autologous HSCT is not more effective than tandem autologous HSCT for patients with standard-risk myeloma.

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

In an approach to reduce NRM associated with allogeneic HSCT, nonmyeloablative conditioning (RIC) methods have been investigated. Most studies are phase 2 studies with no comparison with other treatment modalities. One retrospective study compared myeloablative and nonmyeloablative conditioning. This study, conducted by 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 transplant 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. Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HSCT.

The role of allogeneic HSCT remains controversial, in particular because of conflicting data from cooperative group trials, but also because of improvement in outcomes that have been observed with proteasome inhibitors, new immune modulatory agents, and the use of
posttransplant maintenance therapy. These issues have recently been reviewed and summarized.\textsuperscript{50,51}

**POEMS Syndrome**
A Cochrane review published in 2012 provides a comprehensive source of information on treatment of POEMS.\textsuperscript{11} The authors performed a broad literature search, including CENTRAL (2012, Issue 2), MEDLINE (January 1966 to February 2012), EMBASE (January 1980 to February 2012), and CINAHL Plus (January 1937 to February 2012). They identified no RCTs, no quasi-RCTs, no historically controlled trials or trials with concurrent controls that met their study selection criteria. The Cochrane review included 6 small series of patients (total n=57) who underwent autologous HSCT. Two-year survival rates ranged from 94\% to 100\%. The results suggest that if all published experience with autologous HSCT was pooled, transplant-related mortality would be 3 of 112 (2.7\%). The authors caution that long-term outcomes with autologous HSCT have not been elucidated and require continuing study.

A second 2012 review article indicates case series suggest most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m\textsuperscript{2}.\textsuperscript{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 (VEGF) and radiographic. This author also reports that long-term outcomes with autologous HSCT are unclear given the sparse numbers.

A single-center series published in 2012 from Mayo Clinic reported a 5-year OS of 94\% and a PFS of 75\% among 59 patients entered between 1999 and late 2011.\textsuperscript{52} A second recent series included 9 advanced POEMS syndrome patients who had an Eastern Cooperative Oncology Group performance status score of 3 or 4 and were treated with high-dose melphalan therapy followed by autologous stem cell transplantation from 2004 to 2011.\textsuperscript{53} Eight patients achieved an initial hematologic response, 4 of whom had complete responses. At a median follow-up of 44 months (range, 8-94 months), 7 patients were alive, with 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, despite a hematologic response 3 months after autologous stem cell transplantation. All survivors achieved improvement in general performance status and in clinical response. The responses observed in these patients with advanced POEMS suggest it is a valid treatment option for such cases.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 2.

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Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

### Policy Number
MP-9.044

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<td>NCT01109004</td>
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<td>Myeloma X Relapse (Intensive): A Phase III Study to Determine the Role of a Second Autologous Stem Cell Transplant as Consolidation Therapy in Patients With Relapsed Multiple Myeloma Following Prior High-dose Chemotherapy and Autologous Stem Cell Rescue</td>
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<td>NCT00670631</td>
<td>Tandem Autotransplantation for Multiple Patients With Less Than 12 Months of Preceding Therapy, Incorporating Bortezomib With the Transplant Chemotherapy and During Maintenance</td>
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NCT: national clinical trial.

### Summary of Evidence

**Multiple Myeloma**

The evidence for autologous hematopoietic stem cell transplantation (HSCT) for upfront treatment in patients who have newly diagnosed multiple myeloma includes several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy with high-dose chemotherapy with autologous HSCT. Relevant outcomes include overall survival (OS) and treatment-associated morbidity. In general, the evidence suggests OS rates are improved with autologous HSCT 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 quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for autologous HSCT for treatment of relapsed MM following autologous HSCT or refractory disease includes 1 RCT and a systematic review that summarized data from 4
clinical series of patients who relapsed after a first autologous HSCT. Relevant outcomes include OS and treatment-related morbidity. In general, the evidence suggests OS rates are improved with autologous HSCT 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 quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for tandem autologous HSCT in patients who have MM who fail to achieve at least a near-complete or very good partial response after the first transplant in the tandem sequence (ie, refractory disease) includes 3 RCTs. Relevant outcomes include OS and treatment-related morbidity. The evidence shows tandem autologous HSCT improves OS rates 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 quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for tandem autologous HSCT followed by reduced-intensity conditioning (RIC) allogeneic HSCT in patients who have newly diagnosed MM includes several RCTs comparing RIC-allogeneic HSCT following a first autologous HSCT with autologous transplants, single or in tandem (these studies were based on “genetic randomization,” ie, patients with an HLA-identical sibling were offered an RIC-allogeneic HSCT following the autologous HSCT, whereas the other patients underwent either 1 or 2 autologous transplants). Relevant outcomes include OS and treatment-related morbidity. Although the body of evidence shows inconsistencies in terms of OS and DFS rates, some studies have shown a survival benefit with tandem autologous-RIC allogeneic HSCT, 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 quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for allogeneic HSCT with myeloablative or nonmyeloablative conditioning for upfront or salvage treatment in patients who have MM includes nonrandomized studies. Relevant outcomes include OS and treatment-related morbidity. 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. Nonmyeloablative allogeneic HSCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allogeneic HSCT improves survival compared with autologous HSCT. The evidence is insufficient to determine the effects of the technology on health outcomes.
POEMS Syndrome
The evidence for HSCT of any type in patients who have POEMS syndrome includes case reports and series. Relevant outcomes include OS and treatment-related morbidity. No RCTs of HSCT 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 peritransplant support. However, for patients with disseminated POEMS syndrome, a chain of indirect evidence and contextual factors related to the disease and MM, suggests improvement in health outcomes with autologous HSCT. The evidence is sufficient to determine qualitatively that autologous HSCT results in a meaningful improvement in the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

2013 Input
In response to requests, input was received 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 HSCT is medically necessary for POEMS syndrome, and near-consensus that allogeneic and tandem HSCT is investigational for POEMS syndrome.

2009 Input
In response to requests, input was received from 2 academic medical centers while this policy was under review in 2009. One reviewer agreed with the current policy statement related to tandem autologous/RIC-allogeneic and the other disagreed. Those providing input agreed with the other policy statements. (The conclusion that allogeneic HSCT 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
In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published evidence-based guidelines for the use of HSCT in patients with MM. These guidelines are generally consistent with the conclusions of this evidence review based on published literature through December 31, 2014. ASBMT recognizes that much of the RCT evidence summarized in the 2015 guidelines comes from trials that predate the advent of novel triple therapy induction regimens. Furthermore, advances in supportive care and earlier disease detection has increasingly influenced decision making and allows individual tailoring of therapy. ASBMT guidelines do not address POEMS or other plasma cell dyscrasias besides MM.
Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART)

*Treatment of Newly Diagnosed Multiple Myeloma*\(^{55}\)
The 2012 consensus guideline on the management of newly diagnosed symptomatic MM: updated Mayo Stratification of Myeloma and Risk Adapted Therapy (mSMART) states there is a greater emphasis on delayed high-dose therapy and autologous stem cell transplant (ASCT). With improved induction therapies resulting in deeper responses, many patients are opting to collect their stem cells and delay ASCT while undergoing prolonged induction. Recent evidence has supported this strategy, demonstrating the ongoing benefit of ASCT even when delayed.

*Treatment of Relapsed Multiple Myeloma*\(^{56}\)
Based on the 2012 mSMART multiple myeloma update, if the patient is considered transplant eligible (off-study), risk status should be determined. If the patient is standard risk and relapsed after autologous transplant, repeat autologous transplant is an option, after a bortezomib or immunomodulatory derivative-containing regimen. If the standard-risk patient is relapsed after conventional chemotherapy, the recommendation is to proceed to autologous HSCT or to repeat the previous regimen to maximum response or 1 year. If the patient is high risk and relapses after an autologous transplant, an autologous followed by an allogeneic transplant is an option in selected patients. If a high-risk patient relapses after bortezomib or immunomodulatory-based initial therapy, autotransplant (followed by allogeneic in selected patients), is recommended.

*International Myeloma Working Group*\(^{57}\)
The conclusions and recommendations of the consensus statement on the current status of allogeneic stem cell transplantation for MM are as follows: Myeloablative allogeneic HSCT 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 allogeneic HSCT as first-line therapy is associated with lower TRM but a greater risk of relapse and convincing evidence is lacking that allogeneic HSCT improves survival compared with autologous HSCT.

*National Comprehensive Cancer Network*\(^{58}\)

**Autologous HSCT**
Autologous HSCT is considered a category 1 recommendation as 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.

Repeat autologous HSCT as salvage therapy may be considered for:

- patients initially treated with primary therapy alone followed by the first autologous HSCT when the disease relapsed, who now have progressive disease following the first autologous HSCT (category 2A); and
- patients who have progressive disease after the first autologous HSCT (category 2A).
**Tandem Autologous-Autologous HSCT**

The National Comprehensive Cancer Network Myeloma panel recommends collecting enough stem cells for 2 transplants in all eligible patients. A tandem transplant can be considered for all patients who are candidates for HSCT, and is an option for patients who do not achieve at least a VGPR after the first autologous HSCT (category 2A).

**Allogeneic HSCT**

Myeloablative allogeneic HSCT is an accepted option in the setting of a clinical trial (category 2A) in patients with responsive or primary progressive disease or as salvage therapy in patients with progressive disease following an initial autologous HSCT. Allogeneic HSCT may include nonmyeloablative allogeneic HSCT following an autologous HSCT (category 2A) or myeloablative allogeneic HSCT on a clinical trial (off trial category 3). Current data do not support nonmyeloablative allogeneic HSCT alone.

**POEMS Syndrome**

NCCN guidelines do not address the treatment of POEMS syndrome.  

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

V. **Definitions**

NA

VI. **Benefit Variations**

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. **Disclaimer**

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this
medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered when billed for Poems Syndrome:

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HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR PLASMA CELL DYSCRASIAS, INCLUDING MULTIPLE MYELOMA AND POEMS SYNDROME

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<td>Other disorders of plasma-protein metabolism, not elsewhere classified</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

13. Food and Drug Administration (FDA). Tissue and Tissue Products
Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

### MEDICAL POLICY

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### Medical Policy

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**Other Sources:**


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