Name of Policy:
Single or Tandem Courses of Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

Policy #: 415       Latest Review Date: August 2014
Category: Surgery       Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:  
**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. Bone-marrow 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 and placenta 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).

Immune 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 HLA A, B, and DR loci on each leg 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 Hematopoietic SCT**

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 cause bone marrow failure. The beneficial treatment effect in this procedure results from chemotherapeutic eradication of malignant cells with an associated immune-mediated 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 GVM 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 allogeneic HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation 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 HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.
Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to pre-transplant 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 relatively well-differentiated 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.

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

POEMS Syndrome

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia. 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. 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-1β (IL-1β), IL-6, and tumor...
necrosis factor-α; vascular endothelial growth factor may also be involved. However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in the Table. Both major criteria and at least one of the minor criteria are necessary for diagnosis.

Criteria for the diagnosis of POEMS syndrome

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Known associations</th>
<th>Possible associations</th>
</tr>
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<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
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<tr>
<td>Monoclonal Plasma-proliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
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<td></td>
<td>Organomegaly (spleenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
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<td></td>
<td>Edema (edema, pleural effusion, or ascites)</td>
<td>Polycythemia</td>
<td>Arthralgias</td>
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<td></td>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
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<td></td>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)</td>
<td></td>
<td>Fever</td>
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<td></td>
<td>Papilledema</td>
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<td>Low vitamin B12 values</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. Other large series have been described in the United States and in India. In general, patients with POEMS have a superior overall survival compared with that of MM, nearly 14 years in a large series from the Mayo Clinic. 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 alfa, 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 radiation therapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomatas. Given the underlying plasma cell dyscrasia of
POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.

**Policy:**

**Effective for dates of service on or after August 15, 2013:**

**Multiple Myeloma**

**Autologous hematopoietic stem-cell transplantation (HSCT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat newly diagnosed or responsive* multiple myeloma.

*The term responsive is defined as a tumor showing either a complete, partial, or minimal response. Classifications have been developed to categorize response to induction treatment for patients with multiple myeloma by the EBMT (European Group for Bone and Marrow Transplant), IBMTR (International Bone and Marrow Transplant Research, and ABMTR (Autologous Bone and Marrow Transplant Research). Responses are graded as complete response, partial response, or minimal response. Complete response includes absence of the original monoclonal paraprotein in serum and urine, no increase in size or number of lytic lesions, and disappearance of any soft tissue plasmacytomas. Partial response implies at least a 50% reduction in serum monoclonal paraprotein plus other criteria. The least stringent category, minimal response, requires at least a 25% reduction in serum monoclonal paraprotein and no increase (in size or number) of lytic bone lesions.

**Autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat multiple myeloma patients with primary progressive disease* who are not at high risk.

*Primary progressive disease is progression that occurs during or immediately after the first conventional-dose induction regimen given to a newly diagnosed myeloma patient, i.e., before any HSCT, even before the first transplant cycle in a planned tandem transplant. Patients with primary progressive disease can be categorized as high risk or standard risk. One approach to identifying high-risk patients (other patients are standard risk) is the detection of t(4:14), t(14:16), or 17p deletion by FISH assay, chromosome 13 deletion or hypodiploidy by karyotyping, or plasma cell labeling index greater than 3%; finding one abnormality identifies a patient at high risk. Patients with beta-2-microglobulin levels greater than 5.5 mg per liter are also often considered high risk.

**A second course of autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat responsive myeloma that has relapsed after a durable complete or partial remission following an initial autologous transplant.

**NOTE**: Few patients are considered eligible for a second autotransplant to treat myeloma that has relapsed after a complete or partial remission that followed an initial autotransplant. Nevertheless, retrospective studies report durable complete or partial responses and extended survival for patients treated this way, particularly when a long disease- or progression-free interval followed the first transplant.
**Tandem autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat newly diagnosed or responsive multiple myeloma.

**Tandem transplantation with an initial round of autologous HSCT followed by a non-marrow-ablative conditioning regimen and allogeneic HSCT (i.e., “RIC-transplant”) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat newly diagnosed multiple myeloma patients with an HLA-identical sibling donor and who are in otherwise reasonably good health.

**NOTE**: For patients scheduled for tandem autologous transplants, mobilization before the first cycle usually yields sufficient stem cells to permit two transplant cycles. Response generally is assessed after each treatment cycle for these patients. Evidence summarized here shows that the second transplant extends the duration of survival for those who fail to achieve a complete or very good partial response after the first cycle. However, there appears to be no survival benefit from the second transplant for patients who achieve a complete or very good partial response. In addition, patients who do not have at least stable disease after the first autologous HSCT (i.e., those patients whose disease has progressed with the first autologous HSCT) do not benefit from a second autologous HSCT.

**Autologous HSCT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to treat multiple myeloma in a refractory relapse.

**Monotherapy using allogeneic HSCT does not meet** Blue Cross and blue Shield of Alabama’s medical criteria for coverage and is considered investigational, either as initial therapy of multiple myeloma, or after a prior failed course of autologous HSCT.

**POEMS Syndrome**

**Autologous hematopoietic stem-cell transplantation (HSCT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat disseminated* POEMS syndrome.

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

**Allogeneic and tandem hematopoietic stem-cell transplantation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to treat POEMS syndrome.

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**Effective for dates of service prior to August 15, 2013:**

**Autologous hematopoietic stem-cell transplantation (HSCT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat newly diagnosed or responsive* multiple multiple myeloma.
*The term responsive is defined as a tumor showing either a complete, partial, or minimal response. Classifications have been developed to categorize response to induction treatment for patients with multiple myeloma by the EBMT (European Group for Bone and Marrow Transplant), IBMTR (International Bone and Marrow Transplant Research, and ABMTR (Autologous Bone and Marrow Transplant Research). Responses are graded as complete response, partial response, or minimal response. Complete response includes absence of the original monoclonal paraprotein in serum and urine, no increase in size or number of lytic lesions, and disappearance of any soft tissue plasmacytomas. Partial response implies at least a 50% reduction in serum monoclonal paraprotein plus other criteria. The least stringent category, minimal response, requires at least at 25% reduction in serum monoclonal paraprotein and no increase (in size or number) of lytic bone lesions.

**Autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat multiple myeloma patients with primary progressive disease* who are not at high risk.

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**Tandem autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat newly diagnosed or responsive multiple myeloma.

**Tandem transplantation with an initial round of autologous HSCT followed by a non-marrow-ablative conditioning regimen and allogeneic HSCT (i.e., “RIC-transplant”) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to treat newly diagnosed multiple myeloma patients with an HLA-identical sibling donor and who are in otherwise reasonably good health.

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assessed after each treatment cycle for these patients. Evidence summarized here shows that the second transplant extends the duration of survival for those who fail to achieve a complete or very good partial response after the first cycle. However, there appears to be no survival benefit from the second transplant for patients who achieve a complete or very good partial response. In addition, patients who do not have at least stable disease after the first autologous HSCT (i.e., those patients whose disease has progressed with the first autologous HSCT) do not benefit from a second autologous HSCT.

**Autologous HSCT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to treat multiple myeloma in a refractory relapse.

**Monotherapy using allogeneic HSCT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational, either as initial therapy of multiple myeloma, or after a prior failed course of autologous HSCT.

_Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination._

**Key Points:**

**Multiple Myeloma**

**Treatment Overview**

In the prechemotherapy era, the median survival for a patient diagnosed with multiple myeloma (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 24–30 months and a ten-year survival of 3%. In a large group of patients with newly diagnosed multiple myeloma, 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 HSCT 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 multiple myeloma 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. 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.

Recent reviews highlight the treatment of newly diagnosed myeloma, relapsed, and refractory myeloma. A review of the literature highlights advances in the use of autologous and allogeneic HSCT.

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 multiple myeloma, autologous HSCT 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 study, 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/m2 plus total body irradiation followed by autologous HSCT. The authors reported virtually no difference in outcomes, including response rates, progression-free survival (PFS), and OS.

In five of the seven studies, the superior CR rate translated into a significant increase in PFS. However, in the two 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. Three of the seven studies showed superior OS in the autologous HSCT group.

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

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 2,411 patients enrolled in randomized controlled trials (RCTs) compared standard dose chemotherapy versus myeloablative chemotherapy with single autologous HSCT. 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]: 0.59–0.96) but not OS (hazard of death: 0.92; 95% CI: 0.74–1.13); the odds ratio for treatment-related mortality (TRM) was 3.01 (95% CI: 1.64–5.50) 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 multiple myeloma 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 prior to 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.

**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 (e.g., thalidomide, lenalidomide, and bortezomib, as single agents, in combination with dexamethasone, and in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HSCT.

**Repeat Autotransplant for Relapse after Initial Autotransplant**

An evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from four 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 prior to 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 and colleagues 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 to 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 transplant for Relapse after Initial Autotransplant**
Qazilbash and colleagues 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 to 69 months) for the autologous group, median PFS was 6.8 months and OS 29 months. After a median follow-up of 30 months (range: 13 to 66 months) for the allogeneic group, median PFS was 7.3 months and OS 13 months. On univariate analysis, in the allogeneic group, an interval of greater than one 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).

EBMT reported an analysis of 413 MM patients who received a related or unrelated 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 two or more prior autologous transplants. The median OS and PFS from the time of allogeneic transplantation for the entire population were about 25 and ten months, respectively. Cumulative non-relapse mortality (NRM) at one 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 two 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 one or more autologous transplants.

**Tandem HSCT**
A tandem transplant involves an autologous transplant followed by a preplanned second transplant, either another autologous or a 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-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 months’ 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 (3rd) transplant, 12 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Seven years after diagnosis, patients randomized to tandem transplants had higher probabilities than those randomized to single transplants for event-free (EFS; 20% vs. 10%, respectively; p=0.03), relapse-free (RFS; 23% vs. 13%, respectively; p<0.01), and overall (OS; 42% vs. 21%, respectively; p=0.010) survival. Treatment-related mortality 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 one transplant (OS at seven 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 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 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 (seven-year rate of 60%), as compared with the single-transplantation group (seven-year rate of 47%; p=0.10); conversely, among patients achieving CR or near CR after one 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 similar results to the Attal et al study, in that the benefit of a second transplant was seen only in patients who did not achieve at least a very good PR with the first transplant.

**Tandem Autologous/Reduced-intensity Conditioning (RIC) Allogeneic HSCT**

Several RCTs have been published comparing RIC-allogeneic HSCT following a first autologous HSCT to 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 one or two autologous transplants.

The first published study by Garban and colleagues 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 versus 31.7; p=NS and 47.2 months versus 35; 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 vs. 35 months; p=0.07). Updated results of this population were reported with a reference date of July 2008 by Moreau and colleagues. 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 vs. 21 months, respectively; p=0.88), with a trend toward superior OS in favor of double autologous HSCT (median OS 57 vs. 41 months, respectively; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

One study by Bruno and colleagues 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; p=0.02 and 80 months vs. 54; 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 treatment-related mortality rate at two 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 and colleagues reported the results of a prospective study of 110 patients with MM who failed to achieve at least near-complete remission after a first autologous 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 two 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 two studies, the authors of the Moreau et al study suggest that this is 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 non-uniform 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 study. The authors suggest that the subgroup of high-risk patients with de novo MM may get 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 two prospective Phase III 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 a European Group for Blood and Marrow Transplant (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 (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-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=0.0002). Non-relapse mortality at 36 months was 13% versus 3% (p=0.0004). 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 and colleagues 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 three cycles of systemic therapy for myeloma within the past ten 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 three-year PFS were 43% (95% CI: 36-51) in the auto-allo group and 46% (42-51) in the auto-auto group (p=0.67). OS also did not differ at three years (77% [95%CI 72-84] versus 80% [77-84]; p=0.19). Grade 3-5 adverse events between the two groups were 46% and 42%, respectively. The authors concluded that non-myeloablative 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 considered too high, and this strategy has been almost completely abandoned.

In an approach to reduce non-relapse mortality associated with allogeneic HSCT, nonmyeloablative conditioning (RIC) methods have since been investigated. Most studies are Phase II studies with no comparison to other treatment modalities. One retrospective study compared myeloablative and non-myeloablative conditioning. This study, conducted by the EBMT, found that transplant-related mortality was significantly reduced with RIC but because of a higher relapse/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 avoid 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 post-transplant maintenance therapy. These issues have recently been reviewed and summarized.

**Future direction**

Despite recent advances in the treatment of MM, with new drugs and drug combinations, autologous HSCT, and reduced-intensity allografts, it remains an incurable disease. Future challenges will be how to integrate the best combinations of new and old drugs for initial induction treatments, conditioning regimens, and postinduction maintenance.

**Summary**

Several prospective, randomized trials have been conducted comparing conventional chemotherapy with high-dose therapy and autologous HSCT for patients with newly diagnosed multiple myeloma, and superior complete response rates and prolongation of progression-free and overall survival has been demonstrated with autologous HSCT.
A systematic review that summarized data from four clinical series found that some myeloma patients who relapsed after a first autologous HSCT achieved durable partial or complete remissions after a second autologous HSCT as salvage therapy.

Randomized trials comparing a single autologous to a tandem autologous HSCT have shown improved survival with the use of tandem HSCT, but that the benefit of the second HSCT appears to be limited to patients who did not achieve at least a very good partial response with the first transplant.

The results of trials comparing tandem autologous-reduced-intensity conditioning (RIC) allogeneic HSCT to tandem autologous-autologous have shown conflicting results, although most studies have not shown a survival benefit with tandem autologous-RIC allogeneic, and have shown higher transplant-related mortality. Factors across studies that may account for differing trial results include different study designs, non-uniform preparative regimens, different patient characteristics (including risk stratification) and criteria for advancing to a second transplant. The future of the use of tandem autologous-RIC allogeneic in treating myeloma will depend on additional trials with longer follow-up data.

Allogeneic HSCT with myeloablative conditioning may cure a minority of patients, but is associated with a high transplant-related mortality. Nonmyeloablative allogeneic HSCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse and convincing evidence is lacking that allogeneic HSCT improves survival as compared to autologous HSCT. Therefore, allogeneic HSCT in treating myeloma is considered investigational (except as a component of a tandem autologous-RIC allogeneic HSCT).

**Practice Guidelines and Position Statements**

**Treatment of Newly Diagnosed Multiple Myeloma Based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART):**
If the patient is considered transplant eligible (off-study), risk status should be determined. If the patient is standard risk, after induction therapy, autologous HSCT is recommended (with the option to continue induction therapy if response is good). If patient is not in CR or very good PR after the first autologous HSCT, a second autologous HSCT may be considered. In patients considered high risk, if after four cycles of bortezomib, lenalidomide, and dexamethasone, (especially if the patient is not in CR), autologous HSCT is recommended.

**Treatment of Relapsed Multiple Myeloma Based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART):**
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 one 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 Consensus Statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma:
The conclusions and recommendations are as follows: Myeloablative allogeneic HSCT may cure a minority of patients, but is associated with a high transplant-related mortality (TRM), 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 as compared to autologous HSCT.

2013 National Comprehensive Cancer Network (NCCN) Practice Guidelines

**Autologous single transplant:**
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.

A repeat autologous HSCT as salvage therapy may be considered: 1) in patients initially treated with primary therapy alone followed by the 1st autologous HSCT when the disease relapsed, who now have progressive disease following the first autologous HSCT (Category 2A) and 2) in patients who have progressive disease after the first autologous HSCT (Category 2A).

**Tandem autologous-autologous transplant:**
The NCCN Myeloma panel recommends collecting enough stem cells for two 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 transplant:**
National Comprehensive Cancer Network guidelines consider myeloablative allogeneic HSCT as 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**
No RCTs of hematopoietic stem-cell transplantation (HSCT) have been performed in patients with POEMS syndrome, nor is it likely such studies will ever be performed given the rarity of this condition. Available case reports and series are subject to selection bias, and are heterogeneous with respect to treatment approaches and peri-transplant support. However, for autologous HSCT, a chain of indirect evidence suggests improved health outcomes, as several case studies have reported good clinical responses. In addition, certain contextual factors and strong clinical consensus support that autologous HSCT may be considered medically necessary for disseminated POEMS syndrome. Allogeneic and tandem HSCT are considered investigational to treat POEMS syndrome.
**Practice Guidelines and Position Statements**

**HSCT**

**Treatment of Newly Diagnosed Multiple Myeloma Based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART)**

If the patient is considered transplant eligible (off-study), risk status should be determined. If the patient is standard risk, autologous HSCT is recommended (with the option to continue induction therapy if response is good). If patient is not in CR or very good PR after the first autologous HSCT, a second autologous HSCT may be considered. In patients considered high risk, after 4 cycles of bortezomib, lenalidomide, and dexamethasone, autologous HSCT is recommended. Available online at: www.msmart.org/newly%20diagnosed%20myeloma.pdf.

**Treatment of Relapsed Multiple Myeloma Based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART)**

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, autologous HSCT 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 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. Available online at: msmart.org/relapsed%20myeloma.pdf.

**International Myeloma Working Group Consensus Statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma**

The conclusions and recommendations 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.

**2014 National Comprehensive Cancer Network (NCCN) Practice Guidelines**

**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 1st 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 NCCN 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**
Hematopoietic stem-cell transplantation is not a preventive service.

**Key Words:**
Multiple Myeloma, Myeloablative Chemotherapy, Tandem Transplant, Single Transplant, POEMS**

**NOTE:** FOR POEM, refer to Policy 537 Peroral Endoscopic Myotomy (POEM) for Treatment of Esophageal Achalasia

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Coding:**
CPT codes:

38204-38242  Management/transplant preparation/infusion of hematopoietic progenitor cells code range
HCPCS:

**Q0083-Q0085** Chemotherapy administration code range

**Q2049** Injection, doxorubicin hydrochloride, liposomal, imported
   Lipodox, 10 mg

**Q2050** Injection, doxorubicin hydrochloride, liposomal, not otherwise specified, 10 mg

**J9000-J9999** Chemotherapy drug code range

**S2140** Cord blood harvesting for transplantation, allogeneic

**S2142** Cord blood-derived stem-cell transplantation, allogeneic

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

**References:**


Policy History:
Medical Policy Group, February 2010 (2)
Medical Policy Administration Committee, February 2010
Available for comment February 23-April 8, 2010
Medical Policy Group, December 2011; Updated CPT codes for 2012: 38208, 38209 and added codes 38230 & 38232
Medical Policy Panel, April 2012
Medical Policy Group, February 2013(3): Updated Description, Key Points, and References; no change in policy statement
Medical Policy Panel, August 2013
Medical Policy Group, August 2013(3): Updated Title, Description, Policy Statement, Key Points and References; no change in Multiple Myeloma policy statement; policy statements regarding POEMS syndrome added
Available for comment August 15 through September 28, 2013
Medical Policy Group, January 2014 (1): 2014 Coding Update: added current codes Q2049 and Q2050 to coding section; new codes are included in the chemotherapy drug code range
Medical Policy Panel, August 2014
This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.