MEDICAL POLICY – 8.01.17
Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

BCBSA Ref. Policy: 8.01.17
Effective Date: April 1, 2018
Last Revised: Nov. 1, 2018
Replaces: 8.01.507

RELATED MEDICAL POLICIES:
- 2.01.91 Peroral Endoscopic Myotomy (POEM) for Treatment of Esophageal Achalasia
- 7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells
- 12.04.97 Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Plasma cells are a special type of white blood cell. They are made in the bone marrow, and they make antibodies to fight viral and bacterial infections. Multiple myeloma and POEMS syndrome are two types of bone marrow cancer that affect the plasma cells. These cancers may be treated with various medications and chemotherapy. Sometimes a person may be given a very high dose of chemotherapy followed by a hematopoietic cell transplant. This policy describes when a hematopoietic cell transplant may be medically necessary as part of the treatment of multiple myeloma and POEMS syndrome.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Myeloma</strong></td>
<td></td>
</tr>
<tr>
<td>A single or second (salvage) autologous hematopoietic cell transplantation</td>
<td>A single or second (salvage) autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma.</td>
</tr>
<tr>
<td>Tandem autologous hematopoietic cell transplantation</td>
<td>Tandem autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma in patients who fail to achieve at least a near-complete or very good partial response after the first transplant in the tandem sequence.</td>
</tr>
<tr>
<td></td>
<td>Tandem transplantation with an initial round of autologous hematopoietic cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered medically necessary to treat newly diagnosed multiple myeloma patients.</td>
</tr>
<tr>
<td><strong>POEMS Syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Autologous hematopoietic cell transplantation</td>
<td>Autologous hematopoietic cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome (see Additional Information below).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Myeloma</strong></td>
<td></td>
</tr>
<tr>
<td>Allogeneic hematopoietic cell transplantation</td>
<td>Allogeneic hematopoietic cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered investigational.</td>
</tr>
<tr>
<td><strong>POEMS Syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Allogeneic and tandem hematopoietic cell transplantation</td>
<td>Allogeneic and tandem hematopoietic cell transplantation are considered investigational to treat POEMS syndrome.</td>
</tr>
</tbody>
</table>
### Additional Information

- The International Working Group on Myeloma has updated the European Group for Blood and Marrow Transplant (EBMT) criteria to describe a complete response to Multiple Myeloma (MM) therapy. The criteria include negative immunofixation on the serum and urine; disappearance of soft tissue plasmacytomatas; 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.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
</tbody>
</table>
### Code | Description
--- | ---
38215 | Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230 | Bone marrow harvesting for transplantation; allogeneic
38232 | Bone marrow harvesting for transplantation; autologous
38240 | Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241 | Hematopoietic progenitor cell (HPC); autologous transplantation
38242 | Allogeneic lymphocyte infusions

### HCPCS

| Code | Description |
--- | ---
S2140 | Cord blood harvesting for transplantation, allogeneic
S2142 | Cord blood derived stem cell transplantation, allogeneic
S2150 | Bone marrow or blood-derived stem cell (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

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### Related Information

### Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).

- Some plans may participate in voluntary programs offering coverage for patients participating in NIH-approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.
Description

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. POEMS syndrome, characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes, is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia. Plasma cell dyscrasias are treatable but rarely curable. In some cases, hematopoietic cell transplantation (HCT) is considered as therapy.

Background

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. MM usually evolves from an asymptomatic premalignant stage (termed monoclonal gammopathy of undetermined significance). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival when compared with therapy delivered at the time of symptoms or end-organ damage.\(^1\)\(^-\)\(^2\) In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized and referred to as smoldering MM. The overall risk of disease progression from smoldering to symptomatic MM is 10% per year for the first 5 years, approximately 3% per year for the next 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. No single test establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence suggests it is mediated by an imbalance of proinflammatory cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved.

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.

### 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 plasmaproliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td></td>
<td>Organomegaly (spleenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
</tr>
<tr>
<td></td>
<td>Edema (edema, pleural effusion, or 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, hemangiomata, white nails)</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Papilledema</td>
<td></td>
<td>Low vitamin B12 values</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

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 (OS) compared with that of MM (nearly 14 years in a large series). However, given the rarity of POEMS, no randomized controlled trials (RCTs) of therapies have been reported. Numerous approaches have included
ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HCT support. Optimal treatment involves eliminating the plasma cell clone (eg, by surgical excision or local radiotherapy for an isolated plasmacytoma), or systemic chemotherapy in patients with disseminated disease (eg, 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.

Optimal treatment involves eliminating the plasma cell clone (eg, by surgical excision or local radiotherapy for an isolated plasmacytoma), or systemic chemotherapy in patients with disseminated disease (eg, 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.

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in a separate medical policy (see Related Policies).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) 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 (except umbilical cord blood).

**Conditioning for HCT**

**Conventional Conditioning**

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (eg, 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
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 HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the 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 cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allo-HCT

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 HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

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

In the prechemotherapy era, the median survival for a patient diagnosed with MM was approximately 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 reported during a 24-year period from 1971-1994, with a trend toward improvement during 1995-2000, and a statistically significant benefit in overall survival during 2001-2006.¹ These data suggested that autologous HCT was responsible for the trends during 1995-2000, while novel agents have contributed to the improvement since 2001.²

The introduction of novel agents and better prognostic indicators has been the major advances in the treatment of this disease.¹³,¹⁴ Novel agents such as the proteasome inhibitor bortezomib and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed and refractory myeloma and now have been integrated into first-line regimens.¹³⁻¹⁵ With the introduction of these novel treatments, it is now expected that most patients with MM will respond to initial therapy, and only a small minority will have refractory disease.¹⁶

**Summary of Evidence**

**Newly Diagnosed Multiple Myeloma (MM)**

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

For individuals who have newly diagnosed multiple myeloma who receive tandem autologous HCT, the evidence includes several RCTs. Relevant outcomes include overall survival and treatment-related morbidity. Compared with single autologous HCT, a number of RCTs demonstrated tandem autologous HCT improved OS and recurrence-free survival in newly diagnosed multiple myeloma. The available RCTs compare RIC allogeneic HCT (allo-HCT)
following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on genetic randomization (ie, patients with a human leukocyte antigen-identical sibling who were offered an RIC allo-HCT following autologous HCT), whereas other patients underwent either 1 or 2 autologous transplants. Although the body of evidence has shown inconsistencies in terms of overall survival and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allogeneic HCT, although at a cost of higher transplant-related mortality compared with conventional treatments. Factors across studies that may account for differing trial results include different study designs, nonuniform preparative regimens, different patient characteristics (including risk stratification), and criteria for advancing to a second transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

**Relapsed or Refractory Multiple Myeloma**

For individuals who have relapsed MM after failing an autologous HCT who receive autologous HCT, the evidence includes a RCT, a retrospective study, and a systematic review summarizing data from 4 series of patients who relapsed after a first autologous HCT, and a review summarizing recent studies on a second autologous HCT in relapsed myeloma. Relevant outcomes include overall survival and treatment-related morbidity. Despite some limitations of the published evidence, including patient sample heterogeneity, variability in treatment protocols, and short follow-up periods, the available trial evidence has suggested overall survival rates are improved with autologous HCT compared with conventional chemotherapy in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory MM after failing the first transplant who receive tandem autologous HCT, the evidence includes 3 RCTs and a review. Relevant outcomes include overall
survival and treatment-related morbidity. The evidence has shown tandem autologous HCT improves overall survival rates in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**POEMS Syndrome**

For individuals who have POEMS syndrome who receive HCT, the evidence includes case reports and series. Relevant outcomes include overall survival and treatment-related morbidity. No RCTs of HCT of any type have been performed in patients with POEMS syndrome of any severity, nor is it likely such studies will be performed because of the rarity of this condition. Available case reports and series are subject to selection bias and are heterogeneous concerning treatment approaches and peritransplant support. However, for patients with disseminated POEMS syndrome, a chain of evidence and contextual factors related to the disease and MM would suggest improvement in health outcomes with autologous HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

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

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01671826</td>
<td>Autologous Stem Cell Transplantation for Myeloma Patients Over 65 Years (LATMM)</td>
<td>55</td>
<td>Dec 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01208662</td>
<td>A Randomized Phase III Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib, and Dexamethasone (RVD) to High-dose Treatment With Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients up to 65 Years of Age</td>
<td>660</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT02322320</td>
<td>Continued, Long-Term follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 (BMT)</td>
<td>450</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT00177047</td>
<td>Autologous Transplantation for Multiple Myeloma</td>
<td>363</td>
<td>Jan 2019</td>
</tr>
<tr>
<td>NCT01109004</td>
<td>A Trial of Single Autologous Transplant With or Without Consolidation Therapy Versus Tandem Autologous Transplant With Lenalidomide Maintenance for Patients With Multiple Myeloma (BMT CTN 0702)</td>
<td>750</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT01191060</td>
<td>Randomized Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone to High-Dose Treatment With ASCT in the Initial Management of Myeloma in Patients up to 65 Years of Age</td>
<td>700</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT01208766</td>
<td>A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone (VMP) With High Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma</td>
<td>1500</td>
<td>Apr 2021</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT00670631</td>
<td>Tandem Transplantation in Multiple Myeloma (MM) Patients With &lt;12 Months of Prior Treatment</td>
<td>46</td>
<td>Apr 2014 (completed)</td>
</tr>
<tr>
<td>NCT00998270</td>
<td>Autologous Bone Marrow Transplantation (BMT) Compared With Allogeneic BMT in Multiple Myeloma</td>
<td>185</td>
<td>Oct 2017 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**Clinical Input from Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.
2017 Input

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

2013 Input

In response to requests, 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 HCT is medically necessary for POEMS syndrome, and near-consensus that allogeneic and tandem HCT are investigational for POEMS syndrome.

2010 Input

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

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published evidence-based guidelines on the use of hematopoietic cell transplantation (HCT) in patients with multiple myeloma (MM). ASBMT recognized that much of the evidence from randomized controlled trials summarized in the 2015 guidelines came from trials that predated the novel triple-therapy induction regimens. Furthermore, advances in supportive care and earlier disease detection have increasingly influenced decision making and allow individual tailoring of therapy. ASBMT guidelines did not address POEMS or other plasma cell dyscrasias besides MM.
In 2015, ASBMT, and 3 other groups published joint guidelines based on an expert consensus conference. ⁶³ These guidelines contained the following recommendations for HCT as salvage therapy:

... autologous HCT: (1) In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with HCT as part of salvage therapy should be considered standard; (2) High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months; (3) High-dose therapy and autologous HCT can be used as bridging strategy to allogeneic HCT; (4) The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors; (5) Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short remission (less than 18 months remissions) after primary therapy and (6) Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM [multiple myeloma] relapsing after primary therapy comparing to ‘best non-HCT’ therapy.

Regarding allogeneic HCT... (1) Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Allogeneic HCT should be performed in the context of a clinical trial if possible; (3) The role of post allogeneic HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.

**Mayo Stratification of Myeloma and Risk-Adapted Therapy**

**Treatment of Newly Diagnosed Multiple Myeloma**

The 2013 consensus guideline on the management of newly diagnosed symptomatic multiple myeloma, updating the Mayo Stratification of Myeloma and Risk Adapted Therapy (mSMART), stated there is a greater emphasis on delayed high-dose therapy and autologous cell transplant (ACT). ⁶⁴ With improved induction therapies resulting in deeper responses, many patients are opting to collect their stem cells and delay ACT while undergoing prolonged induction. Recent
evidence has supported this strategy, demonstrating the ongoing benefit of ACT even when delayed.

**Treatment of Relapsed Multiple Myeloma**

Based on the 2012 mSMART multiple myeloma update, if the patient is considered transplant eligible (off-study), risk status should be determined.\(^65\) 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 patients relapse after conventional chemotherapy, the recommendation is to proceed to autologous HCT or to repeat the previous regimen to maximum response or 1 year. If patients have high risk and relapse 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**

The 2010 conclusions and recommendations of the International Myeloma Working Group consensus statement on the current status of allogeneic HCT (allo-HCT) for MM are as follows: Myeloablative allogeneic HCT 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.\(^66\) Nonmyeloablative allo-HCT as first-line therapy is associated with lower TRM but a greater risk of relapse, and convincing evidence is lacking that allo-HCT improves survival compared with autologous HCT.

**National Comprehensive Cancer Network**

**Autologous HCT**

The National Comprehensive Cancer Network (NCCN) guidelines (v.3.2018) consider autologous HCT 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.\(^67\)
**Tandem HCT**

NCCN recommends collecting enough stem cells for 2 transplants in all eligible patients.\(^{67}\)

**Allo-HCT**

NCCN recommends the following for allo-HCT: “Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably on a clinical trial. Current data do not support miniallografting alone” (category 2A).\(^{67}\)

**POEMS Syndrome**

NCCN guidelines do not address the treatment of POEMS syndrome.\(^ {67}\)

**Medicare National Coverage**

Medicare has the following national coverage determination for the use of HCT for MM.\(^ {68}\)

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

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

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

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

**Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

**References**


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>06/12/12</td>
<td>New policy, add to Therapy section. Policy replaces 8.01.507.</td>
</tr>
<tr>
<td>09/10/12</td>
<td>Update coding section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>11/15/12</td>
<td>Reviewed and recommended by OAP, November 2012.</td>
</tr>
<tr>
<td>02/01/13</td>
<td>Update Related Policies, change title of policy 8.01.21.</td>
</tr>
<tr>
<td>02/12/13</td>
<td>Update Related Policies, change title of policy 8.02.02.</td>
</tr>
<tr>
<td>03/20/13</td>
<td>The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.</td>
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<tr>
<td>07/25/13</td>
<td>Update Related Policies. Change title to 8.01.35, and add 8.01.520.</td>
</tr>
<tr>
<td>10/14/13</td>
<td>Replace policy. Policy title changed. Policy updated with literature search through mid-March 2013; no change in multiple myeloma policy statements. POEMS syndrome added, with a medically necessary statement for autologous HCT for disseminated disease; allogeneic and tandem HCT for POEMS are investigational. Reference numbers 1, 6-9, 43 were removed, references 3-11, 47 were added and all were renumbered.</td>
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<tr>
<td>11/20/13</td>
<td>Update Related Policies. Add 2.01.91, and removed 8.01.31 as it was archived.</td>
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<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.29 and 8.01.30.</td>
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<tr>
<td>03/21/14</td>
<td>Update Related Policies. Add 8.01.15 and delete 8.01.514.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and add 8.01.529.</td>
</tr>
<tr>
<td>06/24/14</td>
<td>Update Related Policies. Delete 8.01.42 and add 8.01.530</td>
</tr>
<tr>
<td>11/20/14</td>
<td>Annual Review. Policy updated with literature review through June 15, 2014; no change in policy statements. Reference numbers 2 and 3 were removed; numbers 1, 32, 42, 47, 48, and 50 were added. ICD-9 and ICD-10 diagnosis and procedure codes removed; they do not related to adjudication of the policy.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review through July 14, 2015; references 2-3 were removed, references 16, 32, and 54 were added. Policy statements unchanged. Coding update: CPT codes 38320-21 and 86812-16, 86821-22 removed; these are informational and not reviewed in the scope of this policy.</td>
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<tr>
<td>08/01/16</td>
<td>Annual Review, approved July 12, 2016. No changes to policy statement.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Interim Review, approved December 13, 2016. Policy paragraphs restructured and wording edited for more specific restrictions of HCST for POEMS to autologous transplant only and excluding allogeneic including RIC allogeneic, RIC autologous, and tandem transplantations. HCT for myeloma clarified to explicitly require induction chemotherapy achieving partial response or better prior to HCT for initial treatment</td>
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<tr>
<td>04/01/17</td>
<td>Annual Review, approved March 14, 2017. Policy updated with literature review through July 13, 2016 and results of clinical input; references 21, 48, and 55 added; reference 59 updated. Policy statements became less restrictive in regards to treatment of multiple myeloma.</td>
</tr>
<tr>
<td>06/09/17</td>
<td>Coding update; updated description for CPT codes 38230, 38240, and 38241.</td>
</tr>
<tr>
<td>10/24/17</td>
<td>Policy moved to new format; no change to policy statements.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, removed 8.02.02 from related policies as it was archived.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at: https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW, Room 509F, HHH Building Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD) Complaint forms are available at:

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):
Tsab ntwaw tshaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntwaw tshaj xo no muaj cov ntsiab lus tseem ceeb bokj koi daim ntawv thov kev pab los yoy koi qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnbv tseem ceeb uas rau hauv daim ntawm no. Tej zaum koj koy juaw ta uu qee yam uas peb kom koj uas tit pub dhaus cov caij nyong uas teev rau hauv daim ntawv no mas koi tshaj juaw ta uu basis kev pab cuam kho hobo los yoy kev pab them tej qni kho mbo ntwaw. Koj muaj cai kom laww muab cov ntsiab lus no uas tau muab sau koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Ilokano (Ilocano):
Daytoy a Pakdaad ket naglaon iti Napateg nga Imporsacion. Daytoy a pakdaad marabalin nga adda ket naglaon iti napateg nga imporsacion maianggape iti aplikasyonyo wenn coverage babaen iti Premera Blue Cross. Daytoy ket marabalin dagiti importante a pelsa iti daytoy a pakdaad. Marabalin nga adda rumbeng nga aramidenyo nga addang sakkay dagiti partikular a,n na nga talinsing nga adda tapno mapagtalainalo nga tiker nga tali saun-atyo wenn Coverage tili tolung kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga imporsacion ken tolung ti bukodyo a pagasasao nga awan ti baydayano. Tumawag ti numero nga osa 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Puede que haya fechas claves en este aviso.

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