

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

**Policy # 00060**

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*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.*

*Note: Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom's Macroglobulinemia is addressed separately in medical policy 00138.*

## Multiple Myeloma

### When Services Are Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to treat multiple myeloma (MM) to be **eligible for coverage\*\*** when **ANY** of the following criteria are met:

- Request for a single autologous HCT; **OR**
- Request for a second (salvage) autologous HCT; **OR**
- Request for tandem\*\* autologous-autologous HCT.

**\*\*Tandem transplantation** refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant used as salvage therapy after failure of initial transplantation or relapsed disease.

Based on review of available data, the Company may consider tandem autologous-allogeneic hematopoietic cell transplantation (HCT) to be **eligible for coverage\*\*** when **BOTH** criteria are met:

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- Initial round of autologous HCT will be followed by a non-marrow-ablative conditioning regimen and allogeneic HCT (i.e., reduced-intensity conditioning transplant); **AND**
- Requested to treat individuals with newly diagnosed multiple myeloma.

## When Services Are Considered Not Medically Necessary

The use of autologous hematopoietic cell transplantation (HCT) to treat multiple myeloma (MM) when coverage criteria are not met is considered to be **not medically necessary**.\*\*

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT), myeloablative or nonmyeloablative, as initial therapy of newly diagnosed multiple myeloma (MM) or as salvage therapy to be **not medically necessary**.\*\*

## POEMS Syndrome

## When Services Are Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to treat disseminated POEMS syndrome to be **eligible for coverage**.\*\*

## When Services Are Considered Not Medically Necessary

The use of autologous hematopoietic cell transplantation (HCT) to treat POEMS in other situations (e.g., localized POEMS syndrome) is considered to be **not medically necessary**.\*\*

## When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers allogeneic and tandem hematopoietic cell transplantation (HCT) to treat POEMS syndrome to be **investigational**.\*

## Policy Guidelines

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

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

## **Background/Overview**

### **Multiple Myeloma**

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 18% of all hematologic cancers in the United States. It is treatable but rarely curable. At diagnosis, most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of disease complications.

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*). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage. 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.

### **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome**

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takatsuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia. 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 has suggested it is mediated by an imbalance of proinflammatory cytokines including interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor  $\alpha$ ; 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 mandatory major criteria, at least 1 of the other major criteria, and at least 1 of the minor criteria are necessary for diagnosis.

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**Table 1. Criteria and Associations for POEMS Syndrome**

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

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000 people. Other large series have been described in the United States, France, China, and India. In general, patients with POEMS have superior overall survival (OS) compared with that of MM (nearly 14 years in a large series). However, given the rarity of POEMS, there is a paucity of randomized controlled trial (RCT) evidence for POEMS therapies. Numerous approaches have been tried, including ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon- $\alpha$ , corticosteroids, alkylating agents, tamoxifen, trans-retinoic acid, and high-dose chemotherapy with autologous hematopoietic cell transplantation (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

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POEMS syndrome, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, have also been investigated.

### **Hematopoietic Cell Transplantation**

Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

### **Conditioning for Hematopoietic Cell Transplantation**

#### **Conventional Conditioning**

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

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## **Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Reduced-intensity conditioning regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

## **Multiple Myeloma 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 10-year survival of 3%. In a large group of patients with newly diagnosed MM, there was no difference in OS reported during a 24-year period from 1971 to 1994, with a trend toward improvement from 1995 to 2000, and a statistically significant benefit in OS from 2001 to 2006. These data suggested that autologous HCT was responsible for the trends from 1994 to 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 inhibitors (eg, bortezomib), the monoclonal antibody daratumumab, and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed and refractory myeloma and now have been integrated into first-line regimens. 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.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

The U.S. FDA 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.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration

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approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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

## Summary of Evidence

### Newly Diagnosed Multiple Myeloma

For individuals who have newly diagnosed multiple myeloma (MM) who receive autologous hematopoietic cell transplantation (HCT) as initial treatment, the evidence includes reviews, a retrospective study, several prospective randomized controlled trials (RCTs) that compare high-dose chemotherapy plus autologous HCT to standard chemotherapy regimens or regimens containing newer MM agents, and systematic reviews. Relevant outcomes are overall survival (OS) and treatment-related morbidity. In general, the evidence has suggested OS rates are improved with autologous HCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes, and inconsistency in reporting or collecting outcomes. Recent RCTs comparing high-dose chemotherapy plus autologous HCT to regimens that include novel MM agents have also shown that high-dose chemotherapy plus autologous HCT improves progression-free survival (PFS). Likewise, a systematic review found that autologous HCT plus novel triplet therapy (bortezomib, lenalidomide, and dexamethasone or carfilzomib, lenalidomide and dexamethasone) significantly improves PFS in newly diagnosed MM when compared to triplet therapy alone for consolidation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have newly diagnosed MM who receive tandem autologous HCT, the evidence includes several RCTs and a systematic review. Relevant outcomes are OS and treatment-related morbidity. Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improves OS and recurrence-free survival in newly diagnosed MM. Two recent RCTs found conflicting results on the benefit of tandem autologous HCT versus single autologous HCT; however, the study that found no additional benefit with tandem autologous HCT had a higher rate of nonadherence to the second planned HCT. Differences in initial therapy regimens between trials may also have led to conflicting results. In a systematic review, tandem autologous HCT was associated with a significantly higher complete response rate compared to single autologous HCT; however, no significant differences were observed between the groups in PFS, OS, or overall response rate. Several RCTs and one retrospective study compared reduced-intensity conditioning (RIC) allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on genetic randomization (ie, patients with a human

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leukocyte antigen-identical sibling were offered RIC allo-HCT following autologous HCT, whereas other patients underwent either 1 or 2 autologous transplants). Although the body of evidence has shown inconsistencies regarding OS and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allo-HCT, although at the cost of higher transplant-related mortality compared with conventional treatments. Factors across studies that may account for differing trial results include different study designs, nonuniform preparative regimens, different patient characteristics (including risk stratification), and criteria for advancing to a second transplant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

## **Relapsed or Refractory Multiple Myeloma**

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

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

## **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome**

For individuals who have POEMS syndrome who receive HCT, the evidence includes retrospective cohort studies, case reports, and case series. Relevant outcomes are OS and treatment-related morbidity. No RCTs of HCT of any type have been performed in patients with POEMS syndrome of any severity, nor is it likely such studies will be performed because of the rarity of this condition. Available case reports and series are subject to selection bias and are heterogeneous concerning

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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 an improvement in the net health outcome.

## **Supplemental Information**

### **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

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

#### **2017 Input**

In response to requests, 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 a consensus that allogeneic hematopoietic cell transplantation (HCT) is investigational for newly diagnosed multiple myeloma (MM) and as salvage therapy after primary graft failure and for the 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 Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) syndrome and near-consensus that allogeneic and tandem HCT are investigational for POEMS syndrome.

### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### **American Society of Clinical Oncology**

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

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

### **American Society for Transplantation and Cellular Therapy**

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

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

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

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

Regarding allogeneic HCT... (1) Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or with high-risk features (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

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need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy."

In 2020, the ASTCT published a guideline on indications for HCT and immune effector cell therapy. These guidelines were updated in 2023, although they only focused on CAR-T therapies; no updates were made to HCT recommendations. Regarding plasma cell dyscrasias, the guideline states that MM remains the most common indication for autologous HCT. For rarer plasma cell dyscrasias like POEMS syndrome, autologous HCT may be considered a clinical option on the basis of single-center and registry data. Detailed recommendations in adults can be found in Table 2.

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

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

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

### International Myeloma Working Group

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

### National Comprehensive Cancer Network

#### Autologous Hematopoietic Cell Transplantation

The National Comprehensive Cancer Network (NCCN) guideline for multiple myeloma (v.3.2026) states that autologous HCT is the preferred option after induction therapy in transplant-eligible patients, but a delayed HCT after early stem cell collection and storage is appropriate as well (category 1 recommendation). A repeat HCT can be considered for refractory/progressive disease after primary treatment in patients with prolonged response to initial HCT.

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### **Tandem Hematopoietic Cell Transplantation**

The NCCN guideline for multiple myeloma (v.3.2026) recommends collecting enough stem cells for 2 transplants in younger patients if tandem transplant or salvage transplant would be considered. A tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for HCT and is an option for patients who do not achieve at least a very good partial response after the first autologous HCT and those with high-risk features.

### **Allogeneic Hematopoietic Cell Transplantation**

The NCCN guideline for multiple myeloma (v.3.2026) states the following for allo-HCT: "Allogeneic HCT includes either myeloablative or nonmyeloablative (ie, "mini" transplant) transplants. Allogeneic HCT has been investigated as an alternative to autologous HCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population."

### **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome**

The NCCN guideline for multiple myeloma (v.3.2026) recommends autologous HCT in patients with POEMS syndrome who are eligible as sole therapy or as consolidation therapy after induction therapy.

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

Not applicable.

### **Medicare National Coverage**

Medicare has the following national coverage determination for the use of HCT for MM.<sup>78</sup> "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:

- GVHD (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- (optional) Quality of life?"

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## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

| NCT No.            | Trial Name                                                                                                        | Planned Enrollment      | Completion Date      |
|--------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------|----------------------|
| <i>Ongoing</i>     |                                                                                                                   |                         |                      |
| <i>Unpublished</i> |                                                                                                                   |                         |                      |
| NCT02322320        | Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 (BMT CTN #Q07LT) | 273 (actual enrollment) | Jun 2019 (Completed) |

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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Original Effective Date: 01/28/2002

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Original Effective Date: 01/28/2002

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Original Effective Date: 01/28/2002

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## **Policy History**

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|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12/06/2001 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 01/28/2002 | Managed Care Advisory Council approval                                                                                                                                                                                                                                                              |
| 12/06/2006 | Medical Director review                                                                                                                                                                                                                                                                             |
| 12/20/2006 | Medical Policy Committee approval. Coverage eligibility unchanged.                                                                                                                                                                                                                                  |
| 09/05/2007 | Medical Director review                                                                                                                                                                                                                                                                             |
| 09/19/2007 | Medical Policy Committee approval. Policy statement language regarding tandem transplants in newly diagnosed or responsive multiple myeloma clarified.                                                                                                                                              |
| 09/09/2008 | Medical Director review                                                                                                                                                                                                                                                                             |
| 09/17/2008 | Medical Policy Committee approval. No change to coverage eligibility.                                                                                                                                                                                                                               |
| 09/03/2009 | Medical Policy Committee approval                                                                                                                                                                                                                                                                   |
| 09/16/2009 | Medical Policy Implementation Committee approval. No change to coverage eligibility.                                                                                                                                                                                                                |
| 09/09/2010 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 09/15/2010 | Medical Policy Implementation Committee approval. Policy title changed from “High-Dose Chemotherapy with Stem-Cell Support for Multiple Myeloma” to “Hematopoietic Stem-Cell Transplantation for Multiple Myeloma”. Policy language and statements extensively updated to reflect current practice. |
| 09/01/2011 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 09/14/2011 | Medical Policy Implementation Committee approval. No changes to coverage.                                                                                                                                                                                                                           |
| 09/06/2012 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 09/19/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged.                                                                                                                                                                                                                   |
| 03/04/2013 | Coding updated                                                                                                                                                                                                                                                                                      |
| 10/03/2013 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 10/16/2013 | Medical Policy Implementation Committee approval. Title changed. Coverage for POEMS syndrome added.                                                                                                                                                                                                 |
| 11/06/2014 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 11/21/2014 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                            |
| 03/05/2015 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 03/19/2015 | Medical Policy Implementation Committee approval. Tandem autologous-autologous hematopoietic stem-cell transplantation to treat multiple myeloma clarified.                                                                                                                                         |
| 03/03/2016 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 03/16/2016 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                            |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes                                                                                                                                                                                                                                                       |
| 03/02/2017 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 03/15/2017 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                            |
| 03/01/2018 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 03/21/2018 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                            |
| 03/07/2019 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 03/20/2019 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                            |
| 03/05/2020 | Medical Policy Committee review                                                                                                                                                                                                                                                                     |
| 03/11/2020 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                            |

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|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03/04/2021 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 03/10/2021 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 05/05/2022 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 05/11/2022 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 05/04/2023 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 05/10/2023 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 05/02/2024 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 05/08/2024 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 05/01/2025 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 05/13/2025 | Medical Policy Implementation Committee approval. No change to coverage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 05/07/2026 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 05/13/2026 | Medical Policy Implementation Committee approval. Added “When Services Are Considered Not Medically Necessary” section to policy. Added “The use of autologous hematopoietic cell transplantation (HCT) to treat multiple myeloma (MM) when coverage criteria are not met is considered to be not medically necessary .” Changed this statement to Not Medically Necessary: “Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT), myeloablative or nonmyeloablative, as initial therapy of newly diagnosed multiple myeloma (MM) or as salvage therapy to be not medically necessary .” Added “The use of autologous hematopoietic cell transplantation (HCT) to treat POEMS in other situations (e.g., localized POEMS syndrome) is considered to be not medically necessary.” |

Next Scheduled Review Date: 05/2027

### **Coding**

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type        | Code                                                                                                                                                             |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CPT              | 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38243<br>Delete code effective 06/01/2026: 38242 |
| HCPCS            | S2140, S2142, S2150                                                                                                                                              |
| ICD-10 Diagnosis | All Related Diagnoses                                                                                                                                            |

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

\*\*Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally

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

Policy # 00060

Original Effective Date: 01/28/2002

Current Effective Date: 06/01/2026

recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

**NOTICE:** If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.