MEDICAL POLICY

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR PLASMA CELL DYSCRASIAS, INCLUDING MULTIPLE MYELOMA AND POEMS SYNDROME
POLICY NUMBER	MP 9.044

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	**5/1/2026**

POLICY

Multiple Myeloma

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

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

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

Allogeneic hematopoietic cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POEMS Syndrome

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

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

Policy Guidelines

The International Working Group on Myeloma has updated the European Group for Blood and Marrow Transplant (EBMT) criteria to describe a complete response to 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.

Cross-References:
MP 9.046 Hematopoietic Cell Transplantation for Waldenstrom Macroglobulinemia

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP medical policy manual. The FEP medical policy manual can be found at: fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

DESCRIPTION/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 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. MM usually evolves from an asymptomatic premalignant stage (termed *monoclonal gammopathy of undetermined significance*). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage. 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.

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)-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 one of the minor criteria are necessary for diagnosis.

Table 1. Criteria and Associations for POEMS Syndrome

Mandatory Criteria	• Polyneuropathy • Monoclonal plasma-proliferative disorder
Other Major Criteria	• Castleman disease • Sclerotic bone lesions • Vascular endothelial growth factor elevation
Minor Criteria	• Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy) • Edema (edema, pleural effusion, ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails) • Papilledema • Thrombosis/polycythemia
Other Symptoms and Signs	• Pulmonary hypertension/restrictive lung disease • Clubbing • Thrombotic diatheses • Weight loss • Vitamin B12 deficiency • Diarrhea • Hyperhidrosis

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000. Other large series had been described in the United States, France, China, and India. In general, patients with POEMS have superior overall survival compared with that of MM (nearly 14 years in a large series). However, given the rarity of POEMS, there is a paucity of RCT evidence for POEMS therapies. Numerous approaches have been tried, including ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, 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 (e.g., by surgical excision or local radiotherapy for an isolated plasmacytoma) or systemic chemotherapy in patients with disseminated disease (e.g., medullary disease or multiple plasmacytomas). Given the underlying plasma cell dyscrasia of POEMS syndrome, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide have also been investigated.

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 a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood is discussed in detail in MP-9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.

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

CONDITIONING FOR HCT

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion 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 ability of cytotoxic chemotherapy with or without radiotherapy to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow 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.

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 radiotherapy that 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 *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative as opposed to fully myeloablative (traditional) regimens.

MM TREATMENT OVERVIEW

In the prechemotherapy era, the median survival for a patient diagnosed with MM was approximately 7 months. After the introduction of chemotherapy (e.g., the alkylating agent melphalan in the 1960s), prognosis improved, with a median survival of 24 to 30 months and 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. These data suggested that autologous HCT was responsible for the trends during 1994-2000, while novel agents have contributed to the improvement since 2001.

The introduction of novel agents and better prognostic indicators has been the major advances in the treatment of this disease. Novel agents such as the proteasome inhibitors (e.g., 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.

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.

RATIONALE

SUMMARY OF EVIDENCE

Newly Diagnosed MM

For individuals who have newly diagnosed MM who receive autologous HCT as initial treatment, the evidence includes several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy with high-dose chemotherapy plus autologous HCT to standard chemotherapy regimens or regimens containing newer MM agents. 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. 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. The evidence is sufficient to determine that the technology results in improvement in the net health outcome.

For individuals who have newly diagnosed MM who receive tandem autologous HCT, the evidence includes several RCTs. Relevant outcomes include overall survival and treatment-related morbidity. Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improve s 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. Several RCTs compared reduced-intensity conditioning allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on genetic randomization (i.e., patients with a human leukocyte antigen-identical sibling were offered reduced-intensity conditioning 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 reduced-intensity conditioning 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 with 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 MM

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 multiple myeloma 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.

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 peri-transplant 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.

DEFINITIONS

N/A

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined

by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered; allogeneic hematopoietic cell transplantation for newly diagnosed multiple myeloma or as salvage therapy; allogeneic and tandem hematopoietic cell transplantation for POEMS syndrome:

CPT Codes ®							
38205	38230	38240					

Covered when medically necessary, autologous hematopoietic cell transplantation to treat multiple myeloma and POEMS Syndrome:

Procedure Codes							
S2150	38204	38206	38207	38208	38209	38210	38211
38212	38213	38214	38215	38232	38241		

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POLICY HISTORY

MP 9.044	**02/26/2020 Consensus Review**. No change to the policy statements. References updated.
	02/14/2021 Consensus Review. No change to policy statements. References, summary of evidence, and description/background section updated.
	02/18/2022 Consensus Review. No change to policy statement. Product Variations updated. References reviewed and updated.
	02/24/2023 Consensus Review. Added NCCN statement. No change to policy statement. New references.
	03/28/2024 Consensus Review. No change to policy stance. Reformatted Table 1. New references.

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR PLASMA CELL DYSCRASIAS, INCLUDING MULTIPLE MYELOMA AND POEMS SYNDROME
POLICY NUMBER	MP 9.044

	11/20/2024 Administrative Update. Removed NCCN statement.
	01/22/2025 Consensus Review. No change to policy stance. Updated references.
	02/04/2026 Consensus review. No change to policy stance. Reformatted coding tables, updated disclaimer and references.