

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

<b>Effective Date:</b>	<b>5/1/2023</b>
------------------------	-----------------

[POLICY RATIONALE](#)  
[DISCLAIMER](#)  
[POLICY HISTORY](#)

[PRODUCT VARIATIONS](#)  
[DEFINITIONS](#)  
[CODING INFORMATION](#)

[DESCRIPTION/BACKGROUND](#)  
[BENEFIT VARIATIONS](#)  
[REFERENCES](#)

### I. POLICY

Autologous hematopoietic cell transplantation may be considered **medically necessary** to treat primary systemic amyloidosis.

Allogeneic hematopoietic cell transplantation is considered **investigational** to treat primary systemic amyloidosis. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

***Cross-references:***

**MP 9.001** Placental/Umbilical Cord Blood as a Source of Stem Cells.

### II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

### III. DESCRIPTION/BACKGROUND

[TOP](#)

#### **PRIMARY AMYLOIDOSIS**

The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

diseases are classified on the basis of the type of amyloidogenic protein involved and by the distribution of amyloid deposits. In systemic amyloidosis, the unnatural protein is produced at a site that is remote from the site(s) of deposition, whereas, in localized disease, the amyloid light chain (AL) protein is produced at the site of deposition. Primary or amyloid light chain amyloidosis, the most common type of systemic amyloidosis, has an incidence of approximately 9 to 14 cases per million person-years with approximately 4000 new cases in the US each year.. The typical age at diagnosis is about 50 to 65 years. The amyloidogenic protein in primary amyloidosis is an immunoglobulin light chain or light-chain fragment produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in primary amyloidosis is typically low, ranging from 5% to 10%, this disease also may occur in association with multiple myeloma in 10% to 15% of patients. Deposition of primary amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

### Treatment

Historically, this disease has had a poor prognosis, with a median survival from diagnosis of approximately 12 months, although outcomes have improved with combination chemotherapy using alkylating agents and autologous hematopoietic cell transplantation (HCT). Emerging approaches include the use of immunomodulating drugs (e.g., thalidomide, lenalidomide, pomalidomide) and the proteasome inhibitor, bortezomib. Regardless of the approach, treatment of primary amyloidosis aims at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. The therapeutic index of any chemotherapy regimen is a key consideration in the context of underlying organ dysfunction.

Chemotherapy for the treatment of light chain amyloidosis was introduced in 1972 in the form of melphalan and prednisone. This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies. Survival after oral melphalan with prednisone (typically 12 to 18 months) is longer than for untreated patients or those given older therapies (10 to 14 months), but more effective regimens have been sought. Combination therapy with vincristine, doxorubicin, and dexamethasone, a well-established regimen for myeloma, has been investigated. However, because of its toxicity, vincristine, doxorubicin, and dexamethasone therapy is usually limited to patients without peripheral neuropathy or cardiomyopathy, both common complications of amyloidosis.

Because conventional regimens rarely cure systemic amyloidosis, and because of the close biologic similarity to multiple myeloma, myeloablative chemotherapy with HCT is being investigated for this disease.

### Hematopoietic Cell Transplantation

Hematopoietic cell transplantation refers to in the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone marrow–toxic doses of 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). These cells 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

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy MP 9.001.

### **Autologous HCT**

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. 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 stem 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 response. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

### **Allogeneic HCT**

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. Compatibility is established by typing human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR 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.

The conventional ("classical") practice of allogeneic 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 in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops 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 preengraftment 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, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility to opportunistic infections.

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 conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains variable with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality 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

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

eradicate residual malignant cells. For this evidence review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens

### 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 (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

#### IV. RATIONALE

[TOP](#)

##### SUMMARY OF EVIDENCE

For individuals with primary amyloidosis who receive autologous HCT, the evidence includes a network meta-analysis, a randomized controlled trial, nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity, and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 69.6% of patients, while transplant-related mortality rates have declined significantly in more recent studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity, and treatment-related mortality. Evidence on the use of allogeneic HCT is sparse and has shown high treatment-related mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

#### V. DEFINITIONS

[TOP](#)

NA

#### VI. BENEFIT VARIATIONS

[TOP](#)

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

### VII. DISCLAIMER

[TOP](#)

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

### VIII. CODING INFORMATION

[TOP](#)

**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 to treat primary systemic amyloidosis:**

Procedure Codes							
38205	38230	38240	38242	S2142	S2150		

**Covered when medically necessary, autologous hematopoietic cell transplantation to treat primary systemic amyloidosis:**

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

ICD-10-CM Diagnosis Codes	Description
E85.0	Non-neuropathic heredofamilial amyloidosis
E85.1	Neuropathic heredofamilial amyloidosis
E85.81	Light chain (AL) amyloidosis
E85.82	Wild-type transthyretin-related (ATTR) amyloidosis
E85.89	Other amyloidosis

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

### IX. REFERENCES

[TOP](#)

1. Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation, prognosis, and therapy. *Mayo Clin Proc.* May 1999; 74(5): 490-4. PMID 10319082
2. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood.* Jun 15 2002; 99(12): 4276-82. PMID 12036853
3. Moreau P, Leblond V, Bourquelot P, et al. Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. *Br J Haematol.* Jun 1998; 101(4): 766-9. PMID 9674753
4. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. *J Clin Oncol.* Jul 15 2001; 19(14): 3350-6. PMID 11454882
5. Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood.* May 15 1998; 91(10): 3662-70. PMID 9573002
6. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood.* May 15 2004; 103(10): 3960-3. PMID 14739213
7. Gertz MA, Lacy MQ, Dispenzieri A. Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: a status report. *Bone Marrow Transplant.* Mar 2000; 25(5): 465-70. PMID 10713619
8. Saba N, Sutton D, Ross H, et al. High treatment-related mortality in cardiac amyloid patients undergoing autologous stem cell transplant. *Bone Marrow Transplant.* Oct 1999; 24(8): 853-5. PMID 10516696
9. Cai Y, Xu S, Li N, et al. Efficacy of Chemotherapies and Stem Cell Transplantation for Systemic AL Amyloidosis: A Network Meta-Analysis. *Front Pharmacol.* 2019; 10: 1601. PMID 32063846
10. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med.* Sep 13, 2007; 357(11): 1083-93. PMID 17855669
11. Parmar S, Kongtim P, Champlin R, et al. Auto-SCT improves survival in systemic light chain amyloidosis: a retrospective analysis with 14-year follow-up. *Bone Marrow Transplant.* Aug 2014; 49(8): 1036-41. PMID 24887378
12. Skinner M, Santhorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med.* Jan 20 2004; 140(2): 85-93. PMID 14734330
13. Vesole DH, Perez WS, Akasheh M, et al. High-dose therapy and autologous hematopoietic stem cell transplantation for patients with primary systemic amyloidosis: a Center for International Blood and Marrow Transplant Research Study. *Mayo Clin Proc.* Jul 2006; 81(7): 880-8. PMID 16835967
14. Cibeira MT, Santhorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. *Blood.* Oct 20 2011; 118(16): 4346-52. PMID 21828140

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

15. Madan S, Kumar SK, Dispenzieri A, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. *Blood*. Feb 02 2012; 119(5): 1117-22. PMID 22147893
16. Sanchorawala V, Skinner M, Quillen K, et al. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. *Blood*. Nov 15 2007; 110(10): 3561-3. PMID 17673601
17. D'Souza A, Dispenzieri A, Wirk B, et al. Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study. *J Clin Oncol*. Nov 10 2015; 33(32): 3741-9. PMID 26371138
18. Sharpley FA, Petrie A, Mahmood S, et al. A 24-year experience of autologous stem cell transplantation for light chain amyloidosis patients in the United Kingdom. *Br J Haematol*. Dec 2019; 187(5): 642-652. PMID 31410841
19. Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. *Bone Marrow Transplant*. Oct 2013; 48(10): 1302-7. PMID 23604010
20. Girnius S, Seldin DC, Meier-Ewert HK, et al. Safety and efficacy of high-dose melphalan and auto-SCT in patients with AL amyloidosis and cardiac involvement. *Bone Marrow Transplant*. Mar 2014; 49(3): 434-9. PMID 24317129
21. Jimenez-Zepeda VH, Franke N, Reece DE, et al. Autologous stem cell transplant is an effective therapy for carefully selected patients with AL amyloidosis: experience of a single institution. *Br J Haematol*. Mar 2014; 164(5): 722-8. PMID 24266428
22. Kim SJ, Lee GY, Jang HR, et al. Autologous stem cell transplantation in light-chain amyloidosis patients: a single-center experience in Korea. *Amyloid*. Dec 2013; 20(4): 204-11. PMID 23914780
23. Sanchorawala V, Hoering A, Seldin DC, et al. Modified high-dose melphalan and autologous SCT for AL amyloidosis or high-risk myeloma: analysis of SWOG trial S0115. *Bone Marrow Transplant*. Nov 2013; 48(12): 1537-42. PMID 23852321
24. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. *Br J Haematol*. Feb 2008; 140(4): 365-77. PMID 18162121
25. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. Nov 2015; 21(11): 1863-1869. PMID 26256941
26. Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. *Br J Haematol*. Jan 2015; 168(2): 186-206. PMID 25303672
27. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Systemic Light Chain Amyloidosis. Version 2.2023.
28. D'Sa S, Kersten MJ, Castillo JJ, et al. Investigation and management of IgM and Waldenstrom-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel. *Br J Haematol*. Mar 2017; 176(5): 728-742. PMID 28198999
29. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016.

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR PRIMARY AMYLOIDOSIS</b>
<b>POLICY NUMBER</b>	<b>MP 9.045</b>

30. Blue Cross Blue Shield Association Medical Policy Reference Manual 8.01.42, Hematopoietic Cell Transplantation for Primary Amyloidosis, February 2023.

### X. POLICY HISTORY

[TOP](#)

<b>MP 9.045</b>	<b>CAC 5/20/14</b> Minor. Information on HSCT for Primary Amyloidosis was extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. References updated. Rationale section added.
	<b>CAC 6/2/15</b> Consensus. No change to policy statements. References and rationale updated. Codes reviewed.
	<b>CAC 5/31/16</b> Consensus. No change to policy statements. References and rationale reviewed. Added reference to NCA CAG-00050R for Medicare variation. Coding reviewed.
	<b>Admin update 1/1/17:</b> Product variation section reformatted.
	<b>CAC 7/25/17</b> Consensus review. Policy title revised to “Hematopoietic Cell Transplantation for Primary Amyloidosis per NCCN nomenclature change. No changes to the policy statements. Background, rationale, and references revised. Coding reviewed.
	<b>Admin update 10/1/17:</b> Added new ICD 10 codes effective from 10/1/17 and deleted old ICD 10 codes.
	<b>1/1/18 Admin Update:</b> Medicare variations removed from Commercial Policies.
	<b>4/9/18</b> Consensus review. No change to policy statements. Background and references updated. Rationale condensed to include evidence summary only.
	<b>2/25/19</b> Consensus review. No change to the policy statements. References reviewed.
	<b>02/26/20</b> Consensus review. No change to the policy statements. References reviewed.
	<b>2/5/21</b> Consensus review. No changes to policy statements. Removed diagnosis codes E85.3 and E85.4. References updated.
	<b>3/1/2022</b> Consensus review. No changes to policy statements. No coding changes. Updated background, FEP, references.
	<b>2/9/2023</b> Consensus review. No changes to policy statement. No coding changes. References and background reviewed and updated.

[TOP](#)

*Health care benefit programs issued or administered by Capital Blue Cross and/or its subsidiaries, Capital Advantage Insurance Company<sup>®</sup>, Capital Advantage Assurance Company<sup>®</sup>, and Keystone Health Plan<sup>®</sup> Central. Independent licensees of the Blue Cross BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.*