

## MEDICAL POLICY

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|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>POLICY TITLE</b>     | <b>HEMATOPOIETIC CELL TRANSPLANTATION FOR WALDENSTROM MACROGLOBULINEMIA</b>                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>POLICY NUMBER</b>    | <b>MP 9.046</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>CLINICAL BENEFIT</b> | <input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN.<br><input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS.<br><input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE.<br><input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS.<br><input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET.<br><input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE. |
| <b>Effective date:</b>  | <b>10/1/2026</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

### POLICY

Autologous hematopoietic cell transplantation may be considered **medically necessary** as salvage therapy of chemosensitive Waldenstrom macroglobulinemia.

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

#### **Cross-References:**

**MP 9.042 Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas**

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

### PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital BlueCross 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: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

### DESCRIPTION/BACKGROUND

#### **Waldenström Macroglobulinemia**

Waldenström macroglobulinemia (WM) is a clonal disorder of B lymphocytes that accounts for 1% to 2% of hematologic malignancies, with an estimated 1500 new cases annually in the United States. Symptoms include weakness, headaches, stroke-like symptoms (confusion, loss of coordination), vision problems, excessive bleeding, unexplained weight loss, and frequent infections. The median age of WM patients is 63 to 68 years, with men comprising 55% to 70% of cases. Median survival of WM ranges from 5 to 10 years, with age, hemoglobin concentration, serum albumin level, and  $\beta_2$ -microglobulin level as predictors of outcome.

The Revised European American Lymphoma and World Health Organization classification and a consensus group formed at the Second International Workshop on Waldenström's

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Macroglobulinemia recognize WM primarily as a lymphoplasmacytic lymphoma with an associated immunoglobulin M (IgM) monoclonal gammopathy. The definition also requires the presence of a characteristic pattern of bone marrow infiltration with small lymphocytes demonstrating plasmacytic differentiation with variable cell surface antigen expression. The Second International Workshop indicated no minimum serum concentration of IgM is necessary for a diagnosis of WM.

### Treatment

The goal of therapy for patients with WM is to achieve symptomatic relief and reduce organ damage without compromising quality of life. Treatment of WM is indicated only in symptomatic patients and should not be initiated solely on the basis of serum IgM concentration. Clinical and laboratory findings that indicate the need for therapy of diagnosed WM include a hemoglobin concentration less than 10 g/dL; platelet count less than 100,000/ $\mu$ L; significant adenopathy or organomegaly; symptomatic Ig-related hyperviscosity ( $>50$  g/L); severe neuropathy; amyloidosis; cryoglobulinemia; cold-agglutinin disease; or evidence of disease transformation.

Primary chemotherapeutic options in patients that may undergo autologous hematopoietic cell transplantation (HCT) often combine rituximab with other agents (e.g., dexamethasone, cyclophosphamide, bortezomib, bendamustine), but other agents may also be used including purine analogues (cladribine, fludarabine). Plasma exchange is indicated for acute treatment of symptomatic hyperviscosity.

### Conventional Preparative Conditioning for Hematopoietic Cell Transplantation

The conventional ("classical") practice of allogeneic hematopoietic cell transplantation (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 effect that develops after engraftment of allogeneic stem cells within individuals' bone marrow space. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to individuals who are sufficiently fit medically to tolerate substantial adverse events that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy 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 individual before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are

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susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment but not graft-versus-host disease.

### Reduced-Intensity Conditioning for Allogeneic HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of non-relapse 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 individual condition. Individuals who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For 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 (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

#### SUMMARY OF EVIDENCE

For individuals who have WM who receive HCT, the evidence includes case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Several retrospective series have evaluated HCT for WM. Analyses of registry data have found 5-year overall survival rates of 52% after allogeneic HCT and 68.5% after autologous HCT. The total number of individuals studied is small and there is a lack of published controlled studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained from BCBSA in 2011, and national and international clinical guidelines support the use of autologous HCT as salvage therapy for individuals with chemosensitive Waldenström Macroglobulinemia. Therefore, the evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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### DEFINITIONS

NA

### 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:

| Procedure Codes |       |       |       |  |  |  |  |
|-----------------|-------|-------|-------|--|--|--|--|
| 38205           | 38230 | 38240 | 38242 |  |  |  |  |

#### Covered when medically necessary:

| Procedure Codes |       |       |       |       |       |       |       |
|-----------------|-------|-------|-------|-------|-------|-------|-------|
| 38204           | 38206 | 38207 | 38208 | 38209 | 38210 | 38211 | 38212 |
| 38213           | 38214 | 38215 | 38232 | 38241 | 38243 | S2150 |       |

| ICD-10-CM Diagnosis Code | Description                                                 |
|--------------------------|-------------------------------------------------------------|
| C88.00                   | Waldenstrom macroglobulinemia not having achieved remission |
| C88.01                   | Waldenstrom macroglobulinemia, in remission                 |

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### POLICY HISTORY

|                 |                                                                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>MP 9.046</b> | <b>02/27/2020 Consensus Review.</b> References reviewed. No change to policy statement or coding.                                                                                      |
|                 | <b>02/15/2021 Consensus Review.</b> No change to policy statement. References updated.                                                                                                 |
|                 | <b>07/18/2022 Consensus Review.</b> No change in policy statement. References updated and coding reviewed. NCCN statement added.                                                       |
|                 | <b>03/06/2023 Consensus Review.</b> No change in policy statement. References updated. Coding reviewed.                                                                                |
|                 | <b>02/29/2024 Consensus Review.</b> No change in policy statement. References updated. No coding changes.                                                                              |
|                 | <b>08/16/2024 Administrative Update.</b> New code update. Added ICD-10 codes C88.00 and C88.01. Removed ICD-10 code C88.0. Effective date 10/01/2024.                                  |
|                 | <b>11/20/2024 Administrative Update.</b> Removed NCCN statement.                                                                                                                       |
|                 | <b>01/30/2025 Consensus Review.</b> No change in policy statement. No coding changes.                                                                                                  |
|                 | <b>06/02/2026 Consensus Review.</b> No changes to policy statement. Removed benefit variations. Updated formatting, product variations, disclaimer, and references. No coding changes. |

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