

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>HEMATOPOIETIC CELL TRANSPLANTATION FOR CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA</b>
<b>POLICY NUMBER</b>	<b>MP 9.038</b>

<b>Effective Date:</b>	<b>6/1/2023</b>
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### I. POLICY

Allogeneic hematopoietic cell transplantation may be considered **medically necessary** to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in individuals with markers of poor-risk disease (see Policy Guidelines and Rationale section). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

Autologous hematopoietic cell transplantation is considered **investigational** to treat CLL or SLL. 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.

### Policy Guidelines

**Table 1. Markers of Poor Prognosis in CLL or SLL**

<b>Community Center</b>	<b>Specialized Center</b>
<ul style="list-style-type: none"> <li>• Advanced Rai or Binet stage</li> <li>• Male sex</li> <li>• Atypical morphology or CLL or SLL</li> <li>• Peripheral lymphocyte doubling time &lt;12 mo</li> <li>• CD38-positive</li> <li>• Elevated <math>\beta</math>2-microglobulin level</li> <li>• Diffuse marrow histology</li> <li>• Elevated serum lactate dehydrogenase level</li> <li>• Fludarabine resistance</li> </ul>	<ul style="list-style-type: none"> <li>• IgVh wild type</li> <li>• Expression of ZAP-70 protein</li> <li>• Del(11q22-q23) (loss of ATM genet)</li> <li>• Del(17p13)/variant TP53</li> <li>• Trisomy 12</li> <li>• Elevated serum CD23</li> <li>• Elevated serum tumor necrosis factor-<math>\alpha</math></li> <li>• Elevated serum thymidine kinase</li> </ul>

CLL: chronic lymphocytic leukemia; IgVh: immunoglobulin heavy-chain variable-region; SLL: small lymphocytic lymphoma.

### Staging and Prognosis of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

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Two scoring systems are used to determine stage and prognosis of patients with CLL or SLL. As outlined in Table 2, and Table 3 the Rai and Binet staging systems classify patients into 3 risk groups with different prognoses and are used to make therapeutic decisions.

**Table 2. Rai Classification for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

Rai Stage	Risk	Description	Median Survival, y
0	Low	Lymphocytosis	>10
I	Intermediate	Lymphocytosis + lymphadenopathy	7 to 9
II	Intermediate	Lymphocytosis + splenomegaly ± lymphadenopathy	7 to 9
III	High	Lymphocytosis + anemia ± lymphadenopathy or splenomegaly	1.5 to 5
IV	High	Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy	1.5 to 5

**Table 3. Binet Classification for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

Binet Stage	Description	Median Survival, y
A	≤3 lymphoid areas, normal hemoglobin, and platelets	>10
B	≥3 lymphoid areas, normal hemoglobin, and platelets	7
C	Any number of lymphoid areas, anemia, thrombocytopenia	5

Because prognosis of patients varies within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table 2, according to availability in clinical centers.

The National Comprehensive Cancer Network guideline on CLL/SLL stated the following as unfavorable prognostic factors: DNA sequencing with mutated *TP53* or ≤2% immunoglobulin heavy-chain variable (*IGHV*) mutation; interphase cytogenetics with del17p or deletion of 11q (del11q); or complex karyotype (≥3 unrelated chromosome abnormalities in more than 1 cell on karyotype).

### National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network guidelines (v.2.2023 ) for CLL and small lymphocytic lymphoma (SLL) state the following regarding HCT:

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- "Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule therapy in patients without significant comorbidities."
- "For patients with CLL/SLL with del(17p) or *TP53* mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if complex karyotype [CK] ( $\geq 3$  abnormalities) is present. However, available data suggest that CK ( $\geq 5$  abnormalities) is associated with inferior overall survival [OS] and event-free survival [EFS] following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics."

### Reduced-Intensity Conditioning for Allogeneic HCT

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered as candidates for reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT). These include those patients whose age (typically over 60 years old) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allo-HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC before a second allogeneic HCT if a complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are human leukocyte antigen (HLA)-identical siblings, matched at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Related donors mismatched at a single locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, haploidentical donors - typically a parent or a child of the patient - with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens, have been under investigation as a stem cell source. Most patients will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

#### **Cross-references:**

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

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

## II. PRODUCT VARIATIONS

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

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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

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#### **CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA**

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in blood, bone marrow, lymph nodes, and spleen; in SLL they are generally confined to lymph nodes. The Revised European-American/World Health Organization Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (eg, Richter transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and treatment outcomes are comparable for both diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses, with median survivals of 6 to 10 years; however, the median survival of high-risk CLL or SLL may only be 2 years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural disease history prompted investigation of HCT as a possible curative regimen.

#### **HEMATOPOIETIC CELL TRANSPLANTATION**

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigens (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.

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Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

### Conditioning for HCT

#### ***Conventional Conditioning for HCT***

The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. The slower GVM effect is considered the potentially curative component, but 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 allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic 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 remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

#### ***Reduced-Intensity Conditioning for Allo-HCT***

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in 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 nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-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.

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### 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 the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

### IV. RATIONALE

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#### SUMMARY OF EVIDENCE

For individuals who have CLL/SLL and markers of poor-risk disease who receive allo-HCT, the evidence includes single-arm prospective and registry-based studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data have suggested that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment-related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes randomized controlled trials and a systematic reviews. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup randomized controlled trial has suggested the quality of life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

### V. DEFINITIONS

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**ALLOGENIC** refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient. These cells are harvested from a donor, after verifying the donor and the recipient are well matched with respect to human leukocyte antigens (HLA). Allogeneic cells provide two (2) theoretical advantages: the lack of tumor contamination associated with autologous stem cells, and the possibility of a beneficial graft-versus-tumor effect. Their disadvantage is the risk of graft-versus host disease (GVHD), which increases with great HLA disparity and recipient age.

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**AUTOLOGOUS** refers to originating within an individual, i.e., self-donation. These stem cells are harvested from patients prior to myeloablative therapy.

**REDUCED-INTENSITY ALLOGENIC STEM CELL TRANSPLANTATION** uses lower doses of chemotherapy than standard allogenic transplant, it does not completely inactivate the patient's immune system or treat the ALL as aggressively. Older, sicker patients may be helped with this type of treatment.

**RELAPSED** refers to patients who have achieved remission but later have decreased numbers of normal blood cells and a return of leukemia in their bone marrow

Refractory refers to patients who have residual leukemia cells in their bone marrow even after they receive intensive treatment

### VI. BENEFIT VARIATIONS

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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.

### VII. DISCLAIMER

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*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

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**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.

**Covered when medically necessary:**

Procedure Codes								
S2140	S2142	S2150	38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38230	38240	38242	

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**Investigational; therefore, not covered when used to treat chronic lymphocytic leukemia, or small lymphocytic lymphoma**

Procedure Codes							
38206	38232	38241					

ICD-10-CM Diagnosis Codes	Description
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse

### IX. REFERENCES

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### X. POLICY HISTORY

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<b>MP 9.038</b>	<b>CAC 5/20/14 Minor.</b> Information related to Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation and this separate policy created. No change to policy statements. Policy guidelines added. References updated.
	<b>CAC 6/2/15 Consensus.</b> No change to policy statements. References and rationale updated. Coding reviewed.
	<b>CAC 5/31/16 Consensus.</b> “Hematopoietic stem cell transplantation (HSCT)” was replaced with “hematopoietic cell transplantation (HCT)” in the policy statements and title. There were no further changes to the policy statements. References and rationale updated. Coding reviewed.
	<b>Admin update 1/1/17:</b> Product variation section reformatted.
	<b>CAC 7/25/17 Consensus.</b> Policy statements unchanged. Cross-references, Product Variation, Description/Background, Rationale, and Reference sections updated. Coding reviewed.
	<b>1/1/18 Admin Update:</b> Medicare variations removed from Commercial Policies
	<b>4/9/18 Consensus review.</b> No change to the policy statements. References reviewed. Rationale revised.
	<b>3/8/19 Consensus review,</b> coding updated. No change to the policy statements. References updated.
	<b>4/16/20 Consensus review.</b> No change to policy statement. References updated and coding reviewed.
	<b>2/25/21 Consensus review.</b> No change to policy statement. References updated.
<b>2/8/22 Consensus review.</b> NCCN statement added, no changes to current criteria. Removed table (Table 2). No references added.	
<b>2/22/23 Consensus review.</b> No change to policy stance. Reformatted policy guidelines, updated definitions. New references.	

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