| Subject: Hematopoietic Stem Cell Transplantation for Chronic Lymphoblastic Leukemia (CLL) and small lymphocytic lymphoma (SLL) | Original Effective Date: 7/29/14 |
|---|---|
| **Guidance Number:** MCG-188 | **Revision Date(s):** |

## SUMMARY

*Chronic Lymphoblastic Leukemia and small lymphocytic lymphoma (SLL)*
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, while in SLL they are generally confined to lymph nodes. The Revised European-American/WHO Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity. [23] 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 (e.g., Richter's 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.

In this disorder, lymphocyte counts in the blood are usually greater than or equal to 5,000/mm3 with a characteristic immunophenotype (CD5- and CD23-positive B cells). The clinical course of this disease progresses from an indolent lymphocytosis without other evident disease to one of generalized lymphatic enlargement with concomitant pancytopenia. There is usually an insidious onset, with diagnosis often resulting from incidental blood tests. Symptoms are usually nonspecific, and include fatigue, anorexia, weight loss, dyspnea on exertion, or a sense of abdominal fullness from an enlarging spleen. Late symptoms include susceptibility to bacterial, viral and fungal infection. Complications of pancytopenia, including hemorrhage and infection, represent a major cause of death in these patients. Immunological aberrations, including Coombs-positive hemolytic anemia, immune thrombocytopenia, and depressed immunoglobulin levels may all complicate the management of CLL/SLL. Treatment ranges from periodic observation with treatment of infectious, hemorrhagic, or immunologic complications to a variety of therapeutic options, including steroids, alkylating agents, purine analogs, combination chemotherapy, monoclonal antibodies, and transplantation. For patients with progressing CLL/SLL, treatment with conventional doses of chemotherapy is not curative. Selected patients may be treated with allogeneic stem cell transplantation.

CLL is staged according to 2 common systems, the Rai and Binet. The Rai system has 5 stages of disease advancement from 0 through IV and the Binet system has 3 stages A through C (A overlaps with Rai 0, I, and II; B with I and II; and C with III and IV). Patients in stages I/II are considered as having intermediate-risk / early-stage disease, and those in stages III/IV as having high-risk / advanced-stage disease.

*Stem Cell Transplantation*
Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white

cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

*Donor Lymphocyte Infusion*
Following an allogeneic hematopoietic stem cell transplant, donor lymphocyte infusion is a form of adoptive immunotherapy and may be requested to induce a graft versus leukemia, or graft versus tumor, response without requiring the recipient to undergo additional high-dose chemotherapy. Donor lymphocytes are collected from the original donor through leukapheresis. This collection is an outpatient procedure for the donor. The lymphocytes are then either infused via vein into the recipient or are frozen for a more clinically appropriate time.

*Pretransplant Evaluation*
The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

## RECOMMENDATION

**All transplants must be approved by the Medical Director prior to authorization**

**Members must meet the criteria outlined below for transplantation and the diagnosis must be made by a Hematologist, Oncologist and/or transplant surgeon.**

**Pre-Transplant Evaluation:**

1. General requirements for transplant evaluation include all of the following: [2 4 5 9 14 20]

   - ❑ History and physical examination

- ❑ **Psychosocial evaluation and clearance:** This must be completed and documentation submitted for review before any additional transplant work-up or testing is initiated.
- ❑ Dietary consult and clearance for transplant
- ❑ Disease evaluation ***may*** include all the following:
    - Bone marrow biopsy and/or bone marrow aspiration: must show adequate response to therapy
    - CT scan
    - PET scan
- ❑ Cardiac exam and clearance for transplant: [ALL]
    - Echocardiogram: Ejection fraction > 50%
    - New York Heart Association functional status Class I-II
- ❑ EKG
- ❑ Chest X-ray
- ❑ Performance Status : [ONE]
    - *Karnofsky score 70-100%
    - **Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Neurological exam and clearance for transplant : [ONE]
    - Normal exam by H&P
    - Abnormal neurological exam with positive findings: [ONE]
        - ➢ Lumbar puncture normal cytology
        - ➢ Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Pulmonary function testing: [ALL]
    - diffusion capacity (DLCO) >60%
    - forced expiratory volume (FEV) >60%
    - forced capacity (FVC) >60%
- ❑ Lab studies:
    - Complete blood cell count, liver function tests, kidney profile, coagulation profile (prothrombin time, partial thromboplastin time)
    - HIV testing
    - Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis D, Ebstein-Barr virus (EBV), cytomegalovirus (CMV) serology, syphilis, toxoplasmosis, herpes simplex virus
    - HLA Antibody
    - Blood type
    - Serum creatinine: <1.5mg%
    - creatinine clearance: > 60 ml/min
    - Bilirubin < 2mg%

Within the last 12 months the following is required:

- ❑ Colonoscopy (indicated > age 50 with removal of any polyps if applicable)
- ❑ Dental examination (contact plan for coverage criteria)

- ❑ GYN examination with Pap smear (indicated > age 18) with complete workup and treatment of abnormal results as indicated
- ❑ Mammogram (indicated > age 40) with complete workup and treatment of abnormal results as indicated
- ❑ Osteoporosis screening with DEXA scan: [ONE]
    - cholestatic disorders
    - prolonged corticosteroid therapy
    - postmenopausal women
    - age > 65

| **Karnofsky Performance Score*** [9 12] | |
|---|---|
| Able to carry on normal activity, no evidence of disease | 100% |
| Able to carry on normal activity, minor signs or symptoms of disease | 90% |
| Normal activity with effort, some signs and symptoms of disease | 80% |
| Cares for self, unable to carry on normal activity or to work | 70% |
| Requires occasional assistance from others but able to care for most needs | 60% |
| Requires considerable assistance from others and frequent medical care | 50% |
| Disabled, requires special care and assistance | 40% |
| Severely disabled, hospitalization indicated, death not imminent | 30% |
| Very sick, hospitalization indicated, active support treatment necessary | 20% |
| Moribund | 10% |
| Dead | 0% |

| **Eastern Cooperative Oncology Group (ECOG) Scale**** [9 17] | |
|---|---|
| Fully active, able to carry on all pre-disease performance without restriction | 0 |
| Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work | 1 |
| Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours | 2 |
| Capable of only limited self-care, confined to bed or chair more than 50% of waking hours | 3 |
| Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair | 4 |
| Dead | 5 |

**Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation:** [3 4 6-14 21-35]

1. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** *ablative* [3] *(must be* ≤ 55 years of age *or non-myeloablative* [3] *(must be* ≤ 75 years of age) from a human leukocyte antigen (HLA)-matched donor [24] (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors [24 40] (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized for the treatment of chronic lymphocytic/lymphoblastic leukemia (CLL) and small lymphocytic lymphoma (SLL) when ALL of the following criteria are met: **[ALL]**

- ❑ Responsive to salvage chemotherapy after having failed fludarabine based therapy; and
- ❑ *Rai stage III-IV disease with any of the following high risk factors for relapse: **[ONE]**:
  - High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VHmutational status)
  - Short initial remission
  - Poor initial response
  - Richter's transformation to diffuse large cell lymphoma
  - Leukocyte count greater than 50 x109/L

**AND**

- ❑ None of the following absolute contraindications are present: [NONE] [4]
  - Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
  - Irreversible brain damage or active central nervous system disease
  - Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
  - No behavioral health disorder by history or psychosocial issues: [One]
    - if history of behavioral health disorder, no severe psychosis or personality disorder
    - mood/anxiety disorder must be excluded or treated
    - member has understanding of surgical risk and post procedure compliance and follow-up required

  ***Note:*** Patient's need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

  - No adequate social/family support

*** Rai Staging System** [8]

- **Stage 0:** CLL is characterized by absolute lymphocytosis (>15,000/$mm^3$) without adenopathy, hepatosplenomegaly, anemia, or thrombocytopenia.
- **Stage I**: CLL is characterized by absolute lymphocytosis with lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.
- **Stage II**: CLL is characterized by absolute lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy.
- **Stage III:** CLL is characterized by absolute lymphocytosis and anemia (hemoglobin <11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.
- **Stage IV**: CLL is characterized by absolute lymphocytosis and thrombocytopenia (<100,000/$mm^3$) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

**Criteria for Repeat Allogeneic Stem Cell Transplantation:**

2. ***Hematopoietic Allogeneic stem cell transplantation*** *(ablative or non-myeloablative)* may be authorized after *the first prior stem cell transplantation* has occurred only one time for members with CLL/SLL who meet all of the above criteria for transplant and have any of the following **:[ONE]**

   - ❑ primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; **OR**
   - ❑ failure to engraft*; **AND**
   - ❑ a suitable allogeneic donor has been identified if applicable

   ***Note:** Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 5 x $10^9$/L or > ANC500at any time after transplantation.*[24]

**Criteria for Donor Lymphocyte Infusion (DLI):**

3. ***Donor lymphocyte infusion (DLI)***, ***collection and cryopreservation*** may be authorized following a medically necessary allogeneic hematopoietic stem cell transplant: [18 19 35]

   - ❑ For incomplete chimerism and disease relapse in the setting of incomplete chimerism (defined as incomplete donor stem cell grafting in the recipient's bone marrow);

     **AND**

   - ❑ Donor lymphocytes must be collected from the original hematopoietic stem cell donor

**CONTINUATION OF THERAPY**

A review for any stem cell transplantation procedure is valid for one year from the time the request was approved. Due to potential lengthy organ donor waiting time, an annual review of clinical information should be conducted to evaluate any changes in the member's clinical status.

## COVERAGE EXCLUSIONS

All of the following are excluded from coverage:

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Patients with refractory progressive disease occurring more than 12 months after the discontinuation of treatment [8]
3. Autologous stem cell transplantation in individuals with CLL or SLL
4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered
5. The following absolute contraindications to stem cell transplantation are not covered: [4]
    - ❑ Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
    - ❑ Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
    - ❑ Irreversible brain damage or active central nervous system disease
    - ❑ Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
    - ❑ No behavioral health disorder by history or psychosocial issues: [One]
        - o if history of behavioral health disorder, no severe psychosis or personality disorder
        - o mood/anxiety disorder must be excluded or treated
        - o member has understanding of surgical risk and post procedure compliance and follow-up required

      ***Note:*** Patient's need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

    - ❑ No adequate social/family support

6. Relative contraindications to stem cell transplantation include all of the following: [9]
    - ❑ poor cardiac function (ejection fraction < 50%)
    - ❑ poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to AML
    - ❑ poor renal function (creatinine clearance < 60ml/min)
    - ❑ poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
    - ❑ active central nervous system involvement
    - ❑ presence of human immunodeficiency virus (HIV)
    - ❑ an active infection with any ONE of the following:
        - o hepatitis B virus (HBV)
        - o hepatitis C virus (HCV)
        - o human T-cell lymphotropic virus (HTLV)-1
    - ❑ Karnofsky rating <70% ; OR
    - ❑ Eastern Cooperative Oncology Group (ECOG) performance status >2

## SUMMARY OF MEDICAL EVIDENCE

There are currently no randomized trials that report the outcomes of high-dose chemotherapy (HDC) followed by stem cell transplant compared to conventional therapy however, single-arm prospective and registry-based studies suggests allogeneic HSCT can provide long-term disease control and overall survival in patients with poor-risk disease. A summary of the most relevant medical evidence is outlined below.

In the peer reviewed literature there are six published non-randomized studies involving a total of 328 patients with advanced CLL who underwent reduced-intensity conditioning (RIC) allogeneic HSCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation. [26-31] The majority of patients in these series were pretreated with a median 3–5 courses of prior regimens. Among individual studies, 27%–57% of patients had chemo-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18%–67%) received stem cells from a donor other than an HLA-identical sibling. Reported non-relapse mortality (NRM), associated primarily with graft-versus-host disease (GVHD) and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 years to 5 years. Overall survival rates ranged from 48%–70%, at follow-up that ranged from 2–5 years. Similar results were reported for progression-free survival, 34%–58% at 2–5 years follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HSCT in patients with poor-risk CLL (n=90; median age 53 years, range: 27-65 years), defined as having 1 of the following: refractoriness or early relapse (i.e., less than 12 months) after purine-analog therapy; relapse after autologous HSCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated IgVh status and/or usage of the VH3-21 gene). [28] With a median follow-up of 46 months, 4-year NRM, EFS, and OS were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

A 20-year cohort study by Toze et al. in 2012 reported similar outcomes (OS of 63% at two years and 55% at five years) among a group of 49 consecutive patients treated with allogeneic HSCT who were unresponsive to initial disease treatment. [32]

Karfan et al (2012) [33] conducted a cohort analysis to compare efficacy of reduced-toxicity allogeneic hematopoietic cell transplantation with conventional chemo-(immuno) therapy (CCIT) in patients with relapsed or refractory CLL. By using estimates from a systematic review and by meta-analysis of available published evidence a Markov decision model demonstrated superior outcome for RT-allo-HCT, with a 10-month overall life expectancy (and 6-month quality-adjusted life expectancy (QALE)) advantage over CCIT.

A retrospective study from the EBMT registry analyzed 368 chronic lymphocytic leukemia patients who underwent allogeneic hematopoietic stem cell transplantation. [34] There were 198 human leukocyte antigen (HLA)-identical siblings; among unrelated transplants, 31 were well matched in high resolution (well matched unrelated donor, WMUD), and 139 were mismatched (MM), including 30 matched in low resolution; 266 patients (72%) received reduced-intensity conditioning and 102 (28%) received standard. According to the EBMT risk score, 11% were in scores 1-3, 23% in score 4, 40% in score 5, 22% in score 6 and 4% in score 7. There was no difference in overall survival (OS) at 5 years between HLA-identical siblings (55% (48-64)) and

WMUD (59% (41-84)), P=0.82. In contrast, OS was significantly worse for MM (37% (29-48) P=0.005) due to a significant excess of transplant-related mortality. Also OS worsened significantly when EBMT risk score increased. HLA matching had no significant impact on relapse (siblings: 24% (21-27); WMUD: 35% (26-44), P=0.11 and MM: 21% (18-24), P=0.81); alemtuzumab T-cell depletion and stem cell source (peripheral blood) were associated with an increased risk. In conclusion, the findings support the use of WMUD as equivalent alternative to HLA-matched sibling donors for allogeneic HSCT in CLL, and justify the application of EBMT risk score in this disease.

Professional Organizations

*The National Comprehensive Cancer Network (NCCN)* guidelines for Non-Hodgkin's Lymphoma do not include autologous or tandem HSCT as a therapeutic option in CLL or SLL.[25] NCCN indicates that allogeneic HSCT (conditioning regimen unspecified) may be considered, preferably in a clinical trial, for select patients (those younger than age 70 years with high-risk disease [Rai high risk, or del17p]) or as salvage treatment in those with progressive or relapsed disease.

*Toronto (ON) Cancer Care Ontario Program Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group:* Stem Cell Transplantation for adults with CLL is recommended for the following subsets: [16]

- Allogeneic stem cell transplantation is an option for selected patients with CLL, including those with high-risk cytogenetics who have failed purine analog therapy.
- Autologous stem cell transplantation is not recommended for patients with CLL.
- Qualifying Statement: The management of CLL is in evolution with the emergence of new treatment options, including targeted therapy. These options must be considered when recommending stem cell transplantation.

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

| CPT | Description |
|---|---|
| 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic |
| 38206 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous |
| 38207 | Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage |
| 38208 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing |
| 38209 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing |
| 38210 | Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion |
| 38211 | Transplant preparation of hematopoietic progenitor cells; tumor cell depletion |
| 38212 | Transplant preparation of hematopoietic progenitor cells; red blood cell removal |
| 38213 | Transplant preparation of hematopoietic progenitor cells; platelet depletion |

| | |
|---|---|
| 38214 | Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion |
| 38215 | Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer |
| 38230 | Bone marrow harvesting for transplantation |
| 38240 | Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic |
| 38241 | Bone marrow or blood-derived peripheral stem cell transplantation; autologous |
| 38242 | Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions |

| HCPCS | Description |
|---|---|
| S2140 | Cord blood harvesting for transplantation, allogeneic |
| S2142 | Cord blood derived stem-cell transplantation, allogeneic |
| S2150 | Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition |

| ICD-9 | Description |
|---|---|
| 204.1 | Chronic lymphoid leukemia |

| ICD-10 | Description |
|---|---|
| C91.1-C91.12 | Chronic lymphocytic leukemia of B-cell type |

## RESOURCE REFERENCES


1. Centers for Medicare & Medicaid Services. NCD for Stem Cell Transplantation (110.8.1). 2010. Accessed at: http://www.cms.gov/medicare-coverage-database/
2. National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) 2013 referral guidelines: Recommended Timing for Transplant Consultation. Accessed at: http://marrow.org/Physicians/When_to_Transplant/Referral_Guidelines.aspx
3. UpToDate. Negrin R, Rai K. Hematopoietic cell transplantation in chronic lymphocytic leukemia. July 2014.
4. McKesson InterQual Criteria for Procedures: InterQual Hematopoietic Transplantation, Allogeneic Stem Cell; 2013.
5. Karenes C. National Marrow Donor Program® (NMDP). Evaluating Adult Patients prior to Hematopoietic Stem Cell Transplantation. Accessed at: http://marrow.org/Physicians/When_to_Transplant/Pre-transplant_Evaluation.aspx.
6. DynaMed LLC [website]. Chronic Lymphoblastic Leukemia. Updated June 2014
7. UpTo Date. Rai K. Treatment of relapsed or refractory chronic lymphocytic leukemia. July 2014.

8. National Cancer Institute. Chronic Lymphoblastic Leukemia PDQ 2014. Accessed at: http://www.cancer.gov/cancertopics/pdq/treatment/CLL/healthprofessional
9. UpToDate: Deeg HJ, Sandmaier B. Determining eligibility for allogeneic hematopoietic cell transplantation. July 2014.
10. National Marrow Donor Program. CLL Transplant Outcomes. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Disease-Specific-Indications-and-Outcomes/CLL/
11. National Bone Marrow Donor Program HLA Matching Requirements. Accessed at: http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx
12. UpToDate: Rai K. Overview of the treatment of chronic lymphocytic leukemia. July 2014.
13. UpToDate: Rai K. Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia. July 2014.
14. UpToDate: Cutler C. The approach to hematopoietic cell transplantation survivorship. July 2014.
15. Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78 p. Accessed at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc_stemcell.pdf
16. C Mackall, T Fry, R Gress, K Peggs, J Storek and A Toubert. Background to hematopoietic cell transplantation, including post transplant immune recovery. Bone Marrow Transplant 44: 457-462; doi:10.1038/bmt.2009.255 Accessed at: http://www.nature.com/bmt/journal/v44/n8/full/bmt2009255a.html
17. Eastern Cooperative Oncology Group (ECOG) Performance Status. Accessed at: http://www.ecog.org/general/perf_stat.html
18. Collins RH, Goldstein S, Giralt S, et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant. 2000; 26(5): 511-516. Accessed at: http://www.nature.com/bmt/journal/v26/n5/full/1702555a.html
19. Mackinnon S. American Society of clinical Oncology (ASCO). Donor Lymphocyte Infusion after Allogeneic Stem Cell Transplantation. 2008. Accessed at: http://www.asco.org/ascov2/Education+&+Training/Educational+Book?&vmview=edbk_detail_view&confID=55&abstractID=54
20. National Bone Marrow Donor Program. Keller C, Karanes C. Pretransplant Evaluation. Evaluating Adult Patients Prior to Transplantation. Accessed at: http://marrow.org/Physicians/When_to_Transplant/Pre-transplant_Evaluation.aspx
21. UpToDate: Chao NG. Selection of an umbilical cord blood graft for hematopoietic cell transplantation. July 2014.
22. Gribben J. Stem cell transplantation in chronic lymphocytic leukemia. Biol Blood Marrow Transplant. Jan 2008; 15(1 Suppl): 53–58. Accessed at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668540/
23. Campo E. Swerdlow S et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. May 2011;19:117. Accessed at: http://bloodjournal.hematologylibrary.org/content/117/19/5019?sso-checked=1
24. National Bone Marrow Donor Program. Measuring Engraftment. Accessed at: http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx
25. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Hodgkin's Lymphomas. V2.2014. Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

26. Brown, JR, Kim, HT, Li, S, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. Biol Blood Marrow Transplant. 2006 Oct;12(10):1056-64. PMID: 17084369
27. Delgado, J, Thomson, K, Russell, N, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood. 2006 Feb 15;107(4):1724-30. PMID: 16239425
28. Dreger, P, Brand, R, Hansz, J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. Leukemia. 2003 May;17(5):841-8. PMID: 12750695
29. Khouri, IF, Saliba, RM, Admirand, J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. Br J Haematol. 2007 May;137(4):355-63. PMID: 17456058
30. Schetelig, J, Thiede, C, Bornhauser, M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. J Clin Oncol. 2003 Jul 15;21(14):2747-53. PMID: 12860954
31. Sorror, ML, Storer, BE, Sandmaier, BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol. 2008 Oct 20;26(30):4912-20. PMID: 18794548
32. Toze, CL, Dalal, CB, Nevill, TJ, et al. Allogeneic haematopoietic stem cell transplantation for chronic lymphocytic leukaemia: outcome in a 20-year cohort. Br J Haematol. 2012 Jul;158(2):174-85. PMID: 22640008
33. Kharfan-Dabaja MA(1), Pidala J, et al. Comparing efficacy of reduced-toxicity allogeneic hematopoietic cell transplantation with conventional chemo-(immuno) therapy in patients with relapsed or refractory CLL: a Markov decision analysis. Bone Marrow Transplant. 2012 Sep;47(9):1164-70. doi: 10.1038/bmt.2012.71. Epub 2012 May 7.
34. Michallet M1, Sobh M, Milligan D, Morisset S, et al. The impact of HLA matching on long-term transplant outcome after allogeneic hematopoietic stem cell transplantation for CLL: a retrospective study from the EBMT registry. Leukemia. 2010 Oct ;24(10):1725-31. doi: 10.1038/leu.2010.165. Epub 2010 Aug 12.
35. UpToDate: Negrin C. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation. July 2014.

## DISCLAIMER

***This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.***

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

*The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members.*

CMS does have a NCD called Stem Cell Transplantation (110.8.1)[1] and covers allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of leukemia and leukemia in remission effective for services performed on or after August 1, 1978.