Subject: Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia (ALL)		Original Effective Date: 10/31/12
Policy Number: MCP-118	**Revision Date(s):** 7/29/15, 6/19/19	
Review Date: 12/16/15, 12/14/16, 6/22/17, 6/19/19, 6/17/20, 11/18/20		
MCPC Approval Date: 6/22/17, 6/19/19, 6/17/20		

DISCLAIMER

This Molina Clinical Policy (MCP) 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 exclusion(s) 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 CMS website. 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 Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Acute Lymphoblastic Leukemia

Acute leukemia's comprise a heterogeneous group of neoplastic disorders that arise from malignant transformation of blood-forming, or hematopoietic, stem cells. Malignant transformation typically involves chromosomal rearrangements (translocations), deletions, or additions, which disturb the normal control of cell division, allowing affected cells to multiply without restraint. Clones, or leukemic cells, arising from such transformation particularly influence the development of white blood cells (WBCs), or leukocytes, and rapidly proliferate in the bone marrow, ultimately replacing normal cells and causing anemia, thrombocytopenia, and granulocytopenia. After release into the blood stream, leukemic cells can infiltrate any organ or site and often spread to the liver, spleen, lymph nodes, central nervous system (CNS), and gonads, where they continue to grow and divide, resulting in small tumors, inflammation, and/or organ damage and failure. One of two major types of acute leukemia, acute lymphoblastic leukemia (ALL) involves stem cells that normally become lymphoblasts, the precursors of leukocytes known as lymphocytes and is an aggressive type of leukemia characterized by the presence of too many lymphoblasts or lymphocytes in the bone marrow and peripheral blood. It can spread to the lymph nodes, spleen, liver, central nervous system (CNS), and other organs. Without treatment, ALL usually progresses quickly. ALL occurs in both children and adults and it is the most common type of cancer in children. ALL is believed to arise from malignant transformation of B- or T-cell progenitor cells. It is more commonly seen in children, but can occur at any age. The disease is characterized by the accumulation of lymphoblasts in the marrow or in various extramedullary sites. The World Health Organization (WHO) classifies ALL as either B lymphoblastic leukemia or T lymphoblastic leukemia. B lymphoblastic

leukemia is subdivided by the presence or absence of specific recurrent genetic abnormalities (t(9;22)), MLL rearrangement, t(12;21), hyperdiploidy, hypodiploidy, t(5;14), and t(1;19). Current treatment decisions rely on the immunophenotype (early-pre-B ALL, pre-B ALL, B-cell ALL, or T-cell ALL) and cytogenetics of affected cells. Hematopoietic stem cells transplantation is a treatment method provided to patients with leukemia disorders to rescue the patients from treatment-induced aplasia after high-dose chemotherapy and/or radiotherapy has been administered to eliminate the recipient's immune system. [22 26]

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. [14]

In general, transplants in first remission have a better chance of a good outcome than transplants received later or when the disease is not in remission. For adults, a transplant in first complete remission or early disease offers a higher likelihood of 5-year survival compared to transplants for patients in second remission or with advanced disease. For children the likelihood of 5-year survival is increased for patients who receive a transplant in early or intermediate disease or first or second complete remission compared to patients with advanced disease at the time of transplant. [2]

RECOMMENDATION [1 3 15 16 25-34]

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet UNOS/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

Pre-Transplant Evaluation: [25 33] **Please see MCP-323 Pre-Transplant Evaluation for additional criteria and information.**

Criteria for transplant evaluation include all of the following:

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance:
  - No behavioral health disorder by history or psychosocial issues:
    - ➢ 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

- Adequate family and social support

- ❑ EKG
- ❑ Chest x-ray
- ❑ Cardiac clearance in the presence of any of the following:
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- ❑ 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
- ❑ Performance Status : [ONE]
  - Karnofsky score 70-100%; or
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Lab studies:
  - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - CD4 count >200 cells/mm-3 for >6 months
      - HIV-1 RNA undetectable
      - On stable anti-retroviral therapy >3 months
      - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
    - If abnormal serology need physician plan to address and/or treatment as indicated
  - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- ❑ *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
- ❑ *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- ❑ Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant

- ❑ *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- ❑ *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

Participating Centers of Excellence may waive these criteria

Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation:

1. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** *ablative or non-myeloablative* from a human leukocyte antigen (HLA)-matched donor (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 (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be considered medically necessary for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) when ALL of the following criteria are met: [ALL]

   - ❑ All pre-transplant criteria are met; and
   - ❑ Complete first remission (CR-1) defined by bone marrow biopsy as **[BOTH]**: [25-33]
     - bone marrow is normocellular with no more than 5% blasts; and
     - no signs or symptoms of the disease

     AND

   - ❑ Any of the following high risk factors for relapse**[ONE]**: [25-33]
     - Age: children who are < 1 year or > 9 years & adults who are < 35 years
     - Any of the following chromosome abnormalities: t(4;11), t(1;19), t(8;14), deletion of(7q), trisomy 8, 11q23 (MLL) translocation
     - B-cell immunophenotype (i.e. presence of Mature B cell phenotype (Burkitt's lymphoma)
     - Extramedullary disease outside the bone marrow especially affecting central nervous system
     - Failure to achieve a complete remission within 6 weeks of the start of induction therapy
     - High white blood cell count (WBC) > 50,000 at diagnosis
     - Hypodiploidy: defined as less than 45 chromosomes
     - Minimal residual disease (MRD) positivity following induction
     - Positive Philadelphia chromosome: (t(9;22) or BCR-ABL positive)

     OR

   - ❑ Second or subsequent complete remission (CR-2) following complete first remission (CR-1) defined by bone marrow biopsy as **[BOTH]**: [25-33]
     - bone marrow is normocellular with no more than 5% blasts; and
     - no signs or symptoms of the disease

     OR

   - ❑ Any stage of relapse [25-33]

AND

- ❑ The requesting transplant recipient should not have any of the following **absolute contraindications**:
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  - Systemic and/or uncontrolled infection
  - AIDS (CD4 count < 200cells/mm3)
  - Unwilling or unable to follow post-transplant regimen
    - ◊ Documented history of non-compliance
    - ◊ Inability to follow through with medication adherence or office follow-up
  - Chronic illness with one year or less life expectancy
  - Limited, irreversible rehabilitation potential
  - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
  - No adequate social/family support

- ❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
  - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
  - Smoking, documentation supporting free from smoking for 6 months
  - Active peptic ulcer disease
  - Active gastroesophageal reflux disease
  - CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
  - Obesity with body mass index of >30 kg/m^2 may increase surgical risk
  - Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
  - Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Hematopoietic Autologous Stem Cell Transplantation:

2. ***Hematopoietic Autologous stem cell transplantation*** may be considered medically necessary in adults and children only if the member has acute lymphocytic/lymphoblastic leukemia and all of the following:

   - ❑ All pre-transplant criteria are met; and
   - ❑ Does not have an allogeneic donor or has medical contraindications to an allogeneic transplantation procedure; and
   - ❑ Is in morphologic and cytogenetic first complete remission (CR1) at the time of stem cell harvest; and
   - ❑ Is at high risk for relapse (see criteria under #1 above); and
   - ❑ Should not have any of the absolute contraindications and should be evaluated for any relative contraindications listed above

❑

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

3. ***Hematopoietic Autologous or Allogeneic Stem Cell Transplantation*** *(ablative or non-myeloablative)* may be authorized after the *first prior autologous stem cell transplantation* has occurred only one time, for members with acute lymphocytic/lymphoblastic leukemia who meet all of the above criteria for transplant and have any of the following:**[ONE]**

   ❑ bone marrow relapse: defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after a complete remission as indicated by a peripheral blast count of 5,000 or greater; or
   ❑ 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

   ***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.*[29]

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

❑ If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
   - Presence of no absolute contraindication as listed above;
   - History and physical within the last 12 months;
   - Kidney profile within the last 12 months;
   - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
   - Psychosocial evaluation or update within the last 12 months;
   - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

❑ If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
   - Authorization letter/documentation from previous insurer;
   - Presence of no absolute contraindication as listed above;
   - History and physical within the last 12 months;
   - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
   - Psychosocial evaluation or update within the last 12 months;

- Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

COVERAGE EXCLUSIONS [25-33]

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation or autologous stem cell transplantation when the above criteria are not met.
2. A second or repeat allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive disease.
3. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant.
4. Autologous stem cell transplantation in adults who have refractory ALL or are in second or greater remission.
5. A tandem/sequential HSCT for the treatment of ALL is considered experimental, investigational or unproven.

SUMMARY OF MEDICAL EVIDENCE [2 4-24]

Hematopoietic cell transplantation (HCT) is considered a standard option for patients with higher-risk ALL. Patterns of use of HCT vary between institutions and there is no consensus regarding patient selection, timing of transplantation, and other aspects of the procedure. Outcomes for hematopoietic stem cell transplantation for acute lymphoblastic leukemia (ALL) in children and adults in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information. [2]

Professional Society Guidelines: Several professional society organizations have recommended that Allogeneic SCT is the preferred method of treatment for individuals with ALL who are in first complete remission (CR1) with HLA matched sibling donor, after relapse, and second complete remission (CR2). [23-28]

The National Marrow Donor Program:

- The NMDP recommends that adolescent and young adults age 15-39 years with ALL be referred for consultation for HSCT when the one of the following characteristics are present: primary induction failure, presence of minimal residual disease after initial therapy, first relapse, CR2 and beyond, if not previously evaluated; and high/very high-risk CR1 including: Philadelphia chromosome positive or Philadelphia-like, iAMP21, 11q23 rearrangement, B-cell with poor-risk cytogenetics.

- The NMDP recommends that infants and children up to age 15 years at diagnosis ALL be referred for consultation for HSCT when one of the following characteristics is present: infant at time of diagnosis, primary induction failure, presence of minimal residual disease after initial therapy, first relapse, CR2 and beyond, if not previously evaluated; and high/very high-risk CR1 including: Philadelphia chromosome positive slow-TKI responders or with IKZF1 deletions, Philadelphia-like, iAMP21 and11q23 rearrangement.

- **NCCN Clinical Practice Guidelines in Oncology (2018)** recommend allogenic transplant for patients with PH-positive ALL however, options are limited for those who relapse after transplant. Participation in clinical trials for adults with relapsed/refractory disease after an initial CR for individuals with Ph-negative ALL is recommended. In lieu of an appropriate trial, re-induction, salvage chemotherapy or allogeneic HSCT are recommended treatment options. [24]

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 COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
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
	Cell infusion codes
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
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

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-10	Description: [For dates of service on or after 10/01/2015]
C91.00- C91.92	Acute lymphoblastic leukemia

RESOURCE REFERENCES

Government Agency

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34. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Internal Medicine, Oncology, Hematology. 10/8/12 & again by a practicing MD board certified in Hematology, Oncology. 3/25/19.

Review/Revision History:

10/31/2012: Policy created
7/29/15: The policy was reviewed and updated with revisions made to the pre-transplant criteria, minor revision to the criteria to include any stage of relapse, guideline and reference sections were updated.
12/14/16, 6/22/17: Policy reviewed, no changes
9/13/18: Policy reviewed, no changes to criteria, updated guidelines and references.

6/18/19: Policy reviewed and the high risk criteria for relapse section was revised based on updated guidelines with the following criteria added: minimal residual disease (MRD) positivity following induction, and failure to achieve a complete remission within 6 weeks of the start of induction therapy. General recommendation and summary of medical evidence sections were condensed for ease of application. Guideline and reference sections were updated.
6/17/20: Policy reviewed, no changes to criteria, updated guidelines and references.