Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Acute Lymphocytic/Lymphoblastic Leukemia**

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Coverage Policy

Cigna covers myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) from an appropriately-matched human leukocyte antigen (HLA) donor as medically necessary for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) when ANY of the following criteria are met:

- failed induction therapy
- second or subsequent remission
- late marrow relapse with high tumor load as indicated by a peripheral blast count of 10,000/µL or more
- B-cell lineage ALL with marrow relapse while on treatment or within six months after termination of therapy
- T-cell lineage ALL with marrow relapse
- first remission for adults with poor prognosis**
- first remission for children with high risk of disease relapse***

Cigna covers a second myeloablative allogeneic HSCT from an appropriately-matched HLA donor as medically necessary for the treatment of ALL when relapsed disease occurs more than six months after first allogeneic HSCT.

Cigna covers autologous HSCT for the treatment of ALL as medically necessary in a child who is ineligible for allogeneic HSCT when there is no active disease and EITHER of the following criteria is met:

- first remission with high risk of disease relapse***

- second or later remission

Cigna does not cover ANY of the following procedures for the treatment of ALL because each is considered experimental, investigational or unproven (this list may not be all-inclusive):

- nonmyeloablative allogeneic HSCT in an adult
- tandem (also known as sequential) transplant
- autologous HSCT in an adult

Cigna does not cover HSCT for the treatment of ALL when ANY of the following conditions are present because it is considered not medically necessary (this list may not be all-inclusive):

- active central nervous system (CNS) involvement
- presence of any significant comorbid medical or psychiatric illness which would significantly compromise the clinical care and chances of survival
- advanced age in an adult

Poor prognosis acute lymphocytic/lymphoblastic leukemia in an adult includes ANY of the following criteria:

- longer than four weeks to achieve a complete remission
- age >35 years
- white blood cell count (WBC) greater than 30 X 10^9 /L (30,000/µL) in B-cell lineage ALL
- WBC greater than 50 X 10^9 /L (50,000/µL) in T-cell lineage ALL
- null cell phenotype
- extramedullary disease
- presence of chromosome abnormalities (e.g., t(9;22)(q34;q11) (the Philadelphia chromosome), t(4;11), t(8,14), t(2,8), (8,22), MLL gene (11q23) or t(1;19)
- elevated beta 2 microglobulin
- deletion of chromosome 7
- trisomy 8
- hypodiploidy

***High-risk of disease relapse in a child includes ANY of the following criteria:**

- failure to achieve a complete remission (CR) within four weeks of induction therapy
- high minimal residual disease at end of remission induction
- relapse while on chemotherapy
- first CR lasting < 24 months
- infancy (age younger than one year)
- age ≥ 10 years
- white blood cell count (WBC) > 50,000/mcL
- extramedullary disease
- presence of chromosomal abnormalities (e.g., t(9;22)(q34;q11) (the Philadelphia chromosome), t(4;11), t(8,14), t(1,19), or MLL gene (11q23)
- hypodiploidy
- near-haploid ALL (i.e., 24 to 28 chromosomes)
- acute lymphocytic/lymphoblastic leukemia resulting from prior cancer therapy

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General Background

Acute lymphocytic leukemia (ALL), also known as acute lymphoblastic leukemia and acute lymphoid leukemia, is a heterogeneous group of disorders and one of the most common forms of leukemia. Many cases of ALL can be categorized on the basis of a single characteristic cytogenetic abnormality that affects prognosis.

Abnormalities thought to be associated with unfavorable outcomes are the lack of cALLa, CD10 antigen, B-cell type ALL, CD7+, CD2, and CD5 immunotypes, near haploidy (i.e., 24–28 chromosomes per cell), hypodiploidy (i.e., <45 chromosomes per cell), >65 chromosomes per cell, and MLL gene rearrangements (11q23,). Other chromosomal abnormalities associated with poor prognoses include t(4;11), t(9;22, deletion of chromosome 7 or trisomy 8, and a variety of translocations including t(2;8), t(8;12), and t(8;22)(National Cancer Institute [NCI], 2014a, 2014b). Certain other characteristics are associated with poor prognosis. In children, younger age at diagnosis, higher white blood cell (WBC) counts (e.g., >50,000/µL), the presence of central nervous system (CNS) disease at diagnosis, and the presence of minimal residual disease after therapy have been shown to be negative prognostic factors for the outcome of children with high-risk ALL (NCI, 2014b; Sramkova, 2007). In adults, elevated B2-microglobulin and advanced age are also associated with poor outcomes.

The rate at which the disease enters complete remission (CR) correlates to treatment and survival outcome. Induction chemotherapy is administered to produce a CR in the bone marrow, evidenced by a normocellular marrow with <5% blasts, no signs or symptoms of CNS leukemia or extramedullary infiltration, and normal complete WBC, including differential, hematocrit/hemoglobin levels, and platelet count. In children, therapy is tailored based on the risk of treatment failure; those children who have very good outcomes with modest therapy are spared more aggressive and toxic treatment (NCI, 2014b). Hematopoietic stem-cell transplantation (HSCT) has been proposed as a treatment option for selected individuals with ALL.

Stem Cell Transplantation
Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into an individual. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor).

The selection of an appropriately-matched allogeneic donor source is dependent on several variables including the availability of a human leukocyte antigen (HLA)-identical sibling donor, and stage of disease. It is preferable for donors to have an HLA type that is identical to the recipient due to the potential for increased complications such as graft rejection and graft-versus-host disease; however, only about one-third of individuals who might otherwise be eligible for allogeneic HSCT have an HLA-matched sibling donor. Especially for individuals with high-risk disease, additional appropriate donor sources may include HLA-matched unrelated and HLA partially-matched related donors.

A boost of hematopoietic progenitor or stem cells, also referred to as a hematopoietic stem-cell infusion (HSCI) may be used to facilitate more rapid hematopoietic recovery, graft loss, or loss of chimerism following HSCT. The cell product used for a boost may be a previously cryopreserved cell product that contains stem cells or may alternatively require the donor to undergo additional evaluation, mobilization, and harvest. A boost is not preceded by a preparative regimen, and may be required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HSCI which is typically given days to weeks after reinduction chemotherapy (LeMaistre, 2013).

Contraindications
The presence of any significant co-morbid conditions that would significantly compromise clinical care and chances of survival is a contraindication to transplant. Absolute contraindications to transplantation include active central nervous system (CNS) involvement and the presence of any significant co-morbid medical or psychiatric illness which would significantly compromise the clinical care and chances of survival. Additionally, advanced age in adults is associated with a higher incidence of on the higher prevalence of unfavorable cytogenetics and an increased frequency of medical conditions that affect the ability to tolerate intensive treatment. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)
- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to AML
- poor renal function (creatinine clearance < 50ml/min)
- poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
- active central nervous system involvement

- a pattern of demonstrated patient noncompliance which would place a transplant at serious risk of failure
- presence of human immunodeficiency virus OR an active form of any ONE of the following:

  - hepatitis B virus (HBV)
  - hepatitis C virus (HCV)
  - human T-cell lymphotropic virus (HTLV)-1
  - Karnofsky rating <60% and/or Eastern Cooperative Oncology Group (ECOG) performance status >2

Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT)
Adults: Several randomized controlled trials (RCTs) and case studies have demonstrated improved outcomes with the use of myeloablative allogeneic HSCT in subsets of adults with five-year overall survival (OS) rates of 28%–69% (Cornelissen, 2009; Tomblyn, 2009; Goldstone, 2008; Fielding, 2007; Vey, 2007; Gokbuget, 2006; Oyekunle, 2006; Camera, 2004). Although allogeneic HSCT is generally associated with lower relapse rates and higher cure incidences than either autologous HSCT or chemotherapy, this is partially offset by an increased treatment-related mortality rate due to graft-versus-host disease, veno-occlusive disease of the liver and interstitial pneumonitis (NCI, 2014a; Cornelissen, 2009; Fielding, 2007, Thomas, 2004). A Cochrane systematic review and meta-analysis by Pidala (2011) of 14 eligible studies involving 3157 patients supports matched-sibling donor allogeneic HSCT as the optimal post-remission therapy in individuals with ALL aged 15 years or over. There was a statistically significant overall survival advantage in favor of the donor versus no donor group ($p = 0.01$), as well as significant improvement in disease-free survival in the donor group ($p = 0.004$). Those in the donor group had significant reduction in primary disease relapse ($p= 0.0004$) and significant increase in non-relapse mortality (p0.001).The authors note this therapy offers superior overall survival and disease-free survival, and significantly reduces the risk of disease relapse, but does impose an increased risk of non-relapse mortality**.**

The results of a prospective clinical trial by Goldstone (2008) suggest that a graft-versus-leukemia (GVL) effect may exist, and that the use of a sibling donor allogeneic HSCT as consolidation therapy provides the greatest chance for long term survival for standard risk adult ALL in first remission. This study also suggests that in the absence of a sibling donor, maintenance chemotherapy is preferable to autologous HSCT as postremission therapy (NCI, 2014a).

Patients who experience a relapse after remission can be expected to succumb within one year, even if a second complete remission is achieved. If there are appropriate available donors, hematopoietic stem-cell transplantation (HSCT) may be a consideration (NCI, 2014a; Fielding, 2009). Allogeneic HSCT offers these patients the best chance for long-term disease-free survival (DFS); however, once these individuals are beyond second remission, the results of all allografting procedures worsen considerably, with only 10–15% of patients becoming long-term, disease-free survivors (Redaelli, 2005; Garcia-Manero and Thomas, 2001). Poorer outcome is also noted for adults who have shorter remission durations (e.g., <6 months) after the first allograft compared with those patients whose remission lasts longer than six months. Adults for whom a human leukocyte antigen (HLA) -matched donor is not available are excellent candidates for enrollment in clinical trials that are studying autologous transplantation, immunomodulation, and novel chemotherapeutic or biological agents (NCI, 2014a).

Children: Allogeneic hematopoietic stem-cell transplantation (HSCT) may be performed immediately after recovery from initial induction therapy and may be used as a substitute for multiple cycles of intensive post-remission chemotherapy. Those who undergo HSCT in remission have better outcomes (Klingebiel, 2005). For the two to four percent of children that fail to achieve remission with initial chemotherapy, further attempts at induction chemotherapy are often unsuccessful and prognosis is usually poor.

Although variables exist, several studies have demonstrated improved outcomes with the use of myeloablative allogeneic HSCT compared with autologous HSCT or chemotherapy in selected infants and children with acute lymphocytic//lymphoblastic leukemia (ALL) (Eckert, 2013; Schrauder, 2006; Balduzzi, 2005; Dalle, 2005; Sanders, 2005; Eapin, 2004). Children receiving human leukocyte antigen (HLA)-matched sibling allogeneic HSCT in first complete remission (CR) have disease-fee survival (DFS) rates of 70–80%, with low relapse rates of 0–10%, although some high-risk individuals (e.g., those with Philadelphia 1 positive [Ph1+] ALL) have lower survival rates of 50–65%. Other studies have demonstrated no significant differences in survival outcomes with

allogeneic HSCT (Gupta, 2013; Malempati, 2007; Ribera, 2007; Gaynon, 2006; Badell, 2005). In a meta-analysis by Gupta et al. (2013), data from 13 studies including 2962 patients, excluding Philadelphia chromosome–positive patients, showed a survival benefit for having a matched sibling donor for patients < 35 years of age (p=0.0003) but not for those > 35 years of age (p=0.9) because of the higher absolute risk of nonrelapse mortality for older patients. No differences were noted by risk group. There was a trend toward inferior survival for autograft versus chemotherapy (p=0.06). No beneficial effect of autografting was seen compared with chemotherapy.

Allogeneic HSCT may be the best therapy for individuals who relapse after a complete remission (CR) (NCI, 2014b). HSCT may be considered for children with T-cell ALL and marrow relapse, patients with precursor B-cell ALL and marrow relapse occurring while on treatment or within six months of termination of therapy, and late marrow relapse with high tumor load as indicated by a peripheral blast count of 10,000/μL or more (NCI, 2014b). Overall DFS rates for individuals in second CR range from 40–60% (Steuber, 2003).

For patients relapsing after an allogeneic HSCT for relapsed ALL, a second ablative allogeneic HSCT may be feasible in a subset of children. Among this group, approximately 10% to 30% may achieve long-term event-free survival. Prognosis is more favorable for children with longer duration of remission after the first HSCT and for those with complete remission at the time of second transplantation (NCI, 2014b). However, many patients may be unable to undergo a second HSCT due to failure to achieve remission, early toxic death or severe organ toxicity.

Summary for Allogeneic HSCT: Based on the published peer-reviewed scientific literature allogeneic HSCT may be an effective treatment for selected adults and children with ALL.

Autologous HSCT
Although autologous HSCT results in a lower rate of treatment-related complications and mortality than allogeneic HSCT, the absence of the graft versus leukemia effect, potential leukemia cell contamination of the autologous marrow, and limited ability to eliminate minimal residual disease following the procedure raise barriers to the effectiveness of autologous HSCT. Outcomes associated with autologous HSCT are inferior compared to allogeneic HSCT in a number of studies.

Adults: Evidence from multiple clinical studies and systematic reviews has suggested that autologous HSCT was either of similar effectiveness to or less effective than chemotherapy (Ashfaq, 2010; Goldstone, 2008; Tavemier, 2007; Dhedrin, 2006; Hahn, 2006; Redaelli, 2005; Ribera, 2005; Thomas, 2004); however, it remains a focus of research interest. In contrast to allogeneic bone marrow transplantation (BMT), results for autologous BMT are less effective than maintenance chemotherapy as postremission treatment (5-year OS = 46% for chemotherapy vs. 37% for autologous BMT; p = .03) (Goldstone, 2008). In the randomized multicenter study by Thomas et al. (2004), the use of autologous HSCT did not confer a significant benefit over chemotherapy alone for persons with high-risk ALL. There was a trend toward improved overall survival (OS) in patients who received autologous HSCT versus chemotherapy alone, with three-year OS rates of 44% versus 35%, respectively, and five-year OS rates of 32% and 21%, respectively.

Dhedrin et al. (2006) evaluated the results of autologous HSCT compared with chemotherapy by performing an individual data-based overview analysis. Three-hundred forty-nine patients with acute lymphocytic/lymphoblastic leukemia (ALL) were eligible for randomization to chemotherapy or autologous hematopoietic stem-cell transplantation (HSCT). Using an intent-to-treat analysis, overall (OS) - and disease-free survival (DFS) were not significantly different in the two treatment arms. The cumulative incidence of relapse was 78% versus 66%, respectively, for the chemotherapy and autologous HSCT arms. At 10 years, the estimated OS was 13% versus 20%, respectively, (p=.78) for the chemotherapy and autologous HSCT arms. Estimated DFS were 12% and 20%, respectively. Cumulative incidences of relapse at 10 years were 84% and 76%, respectively, for the chemotherapy and autologous HSCT arms. This analysis failed to demonstrate the benefit of autologous HSCT over chemotherapy.

Children: Autologous HSCT is rarely a treatment option because of the presence of leukemic cells in the blood and marrow; however, it may be an acceptable treatment option for selected children who do not have a human leukocyte antigen (HLA)-identical donor or who are unable to tolerate high-dose therapy. Although some studies demonstrate inferior outcomes with autologous HSCT compared with those achieved with allogeneic HSCT, this therapy may result in improved DFS in selected children with high-risk acute lymphocytic/lymphoblastic

leukemia (ALL) who have experienced complete remission (CR) and for those with high risk of relapse (Ribera, 2006; Sandler, 2006; Badell, 2005).

There are limited data regarding the effectiveness of autologous HSCT for children in relapse or with refractory ALL. Limitations are drug resistance in the leukemia cell clones, lack of significant graft-versus-leukemia (GVL) effect, and difficulty associated with collecting uncontaminated stem cells. The lack of a graft-versus-leukemia reaction results in a higher incidence of disease relapse with autologous HSCT than occurs with allogeneic HSCT.

Summary for Autologous HSCT: The published peer-reviewed scientific literature in the form of large clinical trials does not demonstrate improved outcomes with autologous HSCT compared with allogeneic HSCT or standard-dose chemotherapy for the treatment of adults with ALL. Although data are not robust, autologous HSCT may result in improved DFS in children with high-risk ALL in complete remission or high-risk of relapse. It is considered an acceptable treatment option for selected children who are ineligible for allogeneic HSCT.

Nonmyeloablative Allogeneic HSCT: Non-myeloablative preparative regimens, also known as mini-transplants, are designed to reduce regimen-related toxicities and allow allogeneic HSCT in persons who are older, have comorbid conditions or have toxicities from previous treatment (Maloney, et al., 2002). Randomized controlled trial data are limited regarding the effectiveness of this therapy in adults and children with ALL. Retrospective case studies demonstrate OS rates of 29%–43%, with relapse rates up to 60%. Treatment-related mortality rates range from 21–27% (Mohty, 2008; Guterriez, 2007; Hamaki, 2005; Massenkeil, 2005).

Guterriez et al. (2007) prospectively evaluated the therapeutic value of non-myeloablative conditioning with allogeneic hematopoietic stem-cell transplantation (HSCT) in 43 adults with B-lineage ALL in second CR. Sixty-five percent of the patients had a leukemia relapse after the treatment. The OS was 31%; median survival was 235 days, and treatment-related mortality (TRM) was 21%.

Massenkeil, et al. (2005) retrospectively compared a group of 25 adults with ALL or acute myelogenous leukemia after reduced-intensity conditioning (RIC) to a historical group of 50 matched controls who received high-dose conditioning. Probability of DFS at three years was 43% and 49% for the RIC and high-dose conditioning groups, respectively. OS was 40% and 37%, respectively, for those receiving RIC compared with high-dose conditioning. Relapse rate for patients receiving RIC was 60% compared to patients receiving high-dose conditioning.

These results are supported by a prospective trial of RIC allogeneic HSCT in 33 adults with ALL who were not eligible for conventional myeloablative chemotherapy (Hamaki, et al., 2005). The patient population was heterogeneous for disease status and risk classification. Treatment-related mortality (TRM) was 27% and two-year overall survival (OS) was 29.7%. The one-year progression-free survival rate was 30.6% for those who underwent hematopoietic stem-cell transplantation (HSCT) in first or second complete remission (CR) and 28.6% in patients who underwent HSCT in relapse or induction failure.

Summary for Nonmyeloablative Allogeneic HSCT: Although results are promising, these studies are limited by uncontrolled study design, small sample size, heterogeneity of study population, and short follow-up. Although it remains a topic of research interest the role of non-myeloablative hematopoietic stem-cell transplantation (HSCT) for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) has not yet been established.

Tandem (Sequential) Transplantation
There are scarce data in the published peer-reviewed medical literature to support the safety and effectiveness of tandem (also known as sequential) transplants for the treatment of ALL. At this time the role of this therapy has not yet been established.

Professional Societies/Organizations
National Cancer Institute ([NCI], 2014a, 2014b): Regarding treatment of adults and children with ALL the NCI notes the following:

Adults:

- If there are appropriate available donors and if the patient is younger than 55 years, bone marrow transplantation (BMT) may be a consideration in the management of this disease.
- For an individual with ALL in remission, current standard post-remission therapy includes allogeneic bone marrow transplant.
- Standard treatment options for recurrent adult ALL may include reinduction chemotherapy followed by allogeneic bone marrow transplantation
- An adult with recurrent ALL for whom an HLA-donor is not available are excellent candidates for enrollment in clinical trials that are studying autologous transplantation for recurrent ALL.

Children:

- For infants with MLL translocations, the role of allogeneic stem cell transplant (SCT) during first remission in infants with MLL gene translocations remains controversial. Case series have suggested that allogeneic transplants in first remission may be effective.
- Given the relatively favorable outcome that can be obtained in these patients with chemotherapy regimens used for pediatric ALL, there is no role for the routine use of allogeneic SCT in first remission for adolescents and young adults with ALL.
- Very high-risk patients have also been considered candidates for allogeneic stem cell transplantation in first remission, although it is not clear if outcomes are better with transplantation.
- Treatment options for recurrent childhood ALL with bone marrow relapse includes allogeneic HSCT.
- For patients with T-cell ALL and marrow relapse, outcomes with chemotherapy alone have generally been poor, and these patients are usually treated with allogeneic HSCT in second complete response regardless of time to relapse.
- For patients relapsing after an allogeneic HSCT for relapsed ALL, a second ablative allogeneic HSCT may be feasible. However, many patients will be unable to undergo a second HSCT procedure because of failure to achieve remission, early toxic death, or severe organ toxicity related to salvage chemotherapy.
- Patients with persistent leukemia at the end of the 4-week induction phase have a poor prognosis and may benefit from an allogeneic stem cell transplant once CR is achieved.
- For patients with a late marrow relapse of B-precursor ALL, a primary chemotherapy approach after achievement of CR2 has resulted in survival rates of approximately 50%, and it is not clear whether allogeneic transplantation is associated with superior cure rate.

National Comprehensive Cancer Network™ ([NCCN Guidelines™], 2013): Guidelines for acute lymphoblastic leukemia note that allogeneic HSCT may be appropriate for the following individuals:

Philadelphia (Ph)-chromosome positive ALL:

- For adolescents and young adults ([AYA], 15-39 years), and adults (≥40 years) achieving a complete remission (CR) following initial induction therapy, consolidation with allogeneic HSCT should be considered if a matched donor is available.
- In patients ≤21 years emerging data suggest that allogeneic HSCT may not confer an advantage over chemotherapy combined with tyrosine kinase inhibitors.
- In the absence of an appropriate clinical trial, patients with relapsed/refractory disease may be considered for allogeneic HSCT if a donor is available
- For patients whose disease relapses after initial allogeneic HSCT, other options may include a second allogeneic HSCT and/or donor lymphocyte infusions.

Ph-chromosome negative ALL:

- Allogeneic HSCT in AYA and adults achieving a CR following initial induction therapy if a matched donor is available particularly in patients with residual disease as assessed by Minimal Residual Disease assays, or those with higher-risk cytogenetics (i.e., hypodiploidy, complex karyotype, MLL rearrangements).
- AYA patients experiencing less than a complete remission after initial induction therapy (i.e., primary refractory disease) may be considered for an allogeneic HSCT if a donor is available
- Allogeneic HSCT in AYA and adults with relapsed/refractory disease following an initial CR

The American Society for Blood and Marrow Transplantation (ASBMT): The ASBMT published updated guidelines on the role of cytotoxic therapy with HSCT for the treatment of ALL in adults (Oliansky, 2012). These guidelines include the following recommendations:

- In the absence of a suitable allogeneic donor, autologous HSCT may be an appropriate therapy because of similar survival outcomes and shorter treatment duration when compared with chemotherapy alone, but results in a high relapse rate.
- Myeloablative allogeneic HSCT is an appropriate treatment for adults with ALL in first CR for all disease risk groups
- Allogeneic HSCT provides a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph negative ALL patients compared with less intensive chemotherapy regimens
- In older (35 years), standard risk, Ph-negative ALL patients, a higher transplant-related mortality diminishes the significant survival advantage with allogeneic HSCT.
- In second CR, allogeneic HSCT is recommended over chemotherapy, as a sizeable fraction of patients achieve extended leukemia-free survival compared to chemotherapy alone.
- New data suggest reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but are insufficient to make a recommendation on the use of reduced-intensity conditioning. Thus, reduced-intensity regimens are appropriate only for adult patients with ALL in remission who are unsuited for myeloablative conditioning.
- Evidence supports a recommendation of allogeneic over autologous SCT. There is insufficient evidence, however, to determine if this effect is more apparent in specific risk subgroups, including Ph+ adult ALL.

The American Society for Blood and Marrow Transplantation (ASBMT) also published updated guidelines on the role of cytotoxic therapy with hematopoietic stem-cell transplantation (HSCT) for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) in children. These guidelines include the following recommendations (Oliansky, 2012):

- Based on expert opinion allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered for patients with T-ALL
- Current data do not support allogeneic HSCT when MLL1 ALL is the sole adverse risk factor.
- Based on expert opinion HSCT may be considered for children with hypoploidal ALL
- Allogeneic HSCT is recommended for children with ALL who experience primary induction failure but subsequently achieve a first complete remission (CR).
- Allogeneic HSCT may be considered for children who have been identified by a validated assay as very high risk due to detection of persistent minimal residual disease
- There are no data to support a benefit for autologous HSCT in children. Autologous HSCT is not recommended in first CR, nor is it usual practice in children.
- There are no data to recommend allogeneic HSCT for patients in active relapse with measurable disease.
- Although children with ALL in > third CR have a poor prognosis regardless of treatment, allogeneic HSCT is recommended because it improves survival outcomes.
- Allogeneic HSCT is not recommended for isolated central nervous system relapse in patients with precursor-B ALL because survival of these patients treated with chemotherapy and radiation therapy is equivalent
- There are no data to make a recommendation for, or against allogeneic HSCT for treatment of an isolated testicular relapse.
- Some children with late relapses achieve extended leukemia-free survival with autologous purged stem-cell transplantation (HSCT); however, the evidence is insufficient to determine that this is better than chemotherapy alone. For those with an early relapse, the outcomes with autologous purged HSCT are less promising.
- Outcomes comparing related vs. unrelated donor allogeneic HSCT have not been adequately studied, especially in patients who have had high-resolution typing, and no recommendation can be made at this time
- Outcomes of autologous versus allogeneic HSCT have not been adequately studied and no recommendation can be made at this time.

The National Marrow Donor Program ([NMDP]): The NMDP (1996-2014) recommends that all individuals with ALL be referred for consultation for HSCT early after initial diagnosis including those in first complete remission, primary induction failure or relapse, presence of minimal residual disease after initial or subsequent therapy, and second complete remission and beyond, if not previously evaluated.

The NMDP also recommends that children with high-risk ALL in first complete remission be referred for consultation for HSCT when any of the following characteristics is present: Philadelphia chromosome positive, WBC >100,000 at diagnosis, 11q23 rearrangement, mature B-cell phenotype (Burkitt's lymphoma). The NMDP recommends referral for evaluation for individuals with primary induction failure or relapse, presence of minimal residual disease after initial or subsequent therapy, or second complete remission and beyond, if not previously evaluated

Use Outside of the US: No relevant information.

Summary
Evidence in the published peer-reviewed scientific literature supports the safety and effectiveness of myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) from an appropriately-matched donor for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) in selected individuals. Although data are not robust, the published peer-reviewed scientific literature also supports the effectiveness of autologous HSCT in selected children with ALL who are ineligible for allogeneic HSCT; however, there is insufficient evidence to support improved health outcomes for adults.

The published peer-reviewed scientific literature does not support the effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of adults or children with ALL who have certain conditions that may affect outcomes to transplantation including active central nervous system (CNS) involvement, the presence of any significant co-morbid illness that would significantly compromise the patient's clinical care and chances of survival, or advanced age in adults.

There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and effectiveness of non-myeloablative allogeneic or tandem hematopoietic stem-cell transplantation (HSCT) for the treatment of individuals with acute lymphocytic/lymphoblastic leukemia (ALL). The role of these therapies has not yet been established.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

CPT®* Codes	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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS Codes	**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

***Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.**

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