Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Acute Myelogenous Leukemia**

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Table of Contents

Hyperlink to Related Coverage Policies

Donor Lymphocyte Infusion
Stem-Cell Transplantation for Myelodysplastic Syndrome
Transplantation Donor Charges
Umbilical Cord Blood Banking

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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 myelogenous leukemia (AML) when ANY of the following criteria is met:

- first remission for a high-risk** individual
- second or subsequent remission
- failed induction
- no induction treatment and any of the following:
  - antecedent hematological disease
  - treatment-related secondary AML

Cigna covers a second myeloablative allogeneic HSCT from an appropriately-matched HLA donor as medically necessary for the treatment of AML when BOTH of the following criteria are met:

- relapse of disease occurring more than six months after first allogeneic HSCT
- second or subsequent remission

Cigna covers reduced-intensity or non-myeloablative allogeneic HSCT as medically necessary for the treatment of AML when the criteria for an allogeneic HSCT are met but a myeloablative regimen is contraindicated because of age or comorbidity.

Cigna covers autologous HSCT as medically necessary for the treatment of AML for whom allogeneic HSCT is not available or is not appropriate when EITHER of the following criteria is met:

- first remission for a high risk* individual
- second or subsequent remission

Cigna does not cover tandem HSCT for the treatment of AML because it is considered experimental, investigational or unproven.

***High-risk includes ANY of the following:**

- requiring more than one cycle to achieve remission
- disease refractory to chemotherapy
- white blood cell (WBC) count > 100,000/ml^3
- French-American-British (FAB) subtype M4 and M5
- chromosome translocations t(10;11), t(1;22), t(6;9), t(9;22)
- abnormalities of chromosome 7 or 5, the long arm of chromosome 3, or 11q23
- trisomy 8
- antigen CD34 and/or P-glycoprotein (MDR1 gene product)
- internal tandem duplication mutations of the FLT3 gene
- history of CNS involvement
- systemic infection at diagnosis
- treatment-induced AML
- history of myelodysplastic syndrome

General Background

Acute myelogenous leukemia (AML), also known as acute granulocytic leukemia, acute myeloid leukemia and acute nonlymphocytic leukemia (ANLL), is a malignancy of the blood-forming tissues of the bone marrow resulting from acquired genetic damage. In most cases, the cause of AML is unknown; however, several factors are thought to be associated with an increased risk for the disease including the use of chemotherapy for the treatment of other cancers (Leukemia & Lymphoma Society, 2012).

Two systems are commonly used to classify AML. The French-American-British (FAB) Cooperative Group classification is based on morphological-histochemical cell characteristics and identifies eight subtypes of AML, categorized as M0-M7. The newer, World Heath Organization Classification System incorporates clinical, morphologic, immunophenotypic, cytogenetic and molecular markers that can be used to direct treatment.

Factors that may be predictive of increased morbidity and mortality include central nervous system involvement with leukemia, systemic infection at diagnosis, elevated white blood count (i.e., >100,000 mm^3), treatment-induced AML and history of myelodysplastic syndrome. Additionally, certain gene and cytogenetic abnormalities have been identified as high-risk for a poor prognosis with chemotherapy. These include internal tandem duplication of the FLT3 gene, deletions of the long arms or monosomies of chromosomes 5 or 7; translocations or inversions of chromosome 3, t(6;9), t(9;22) and abnormalities of chromosome 11q23, t(10;11) translocation, t(1;22)(p13;q13) translocation, trisomy 8, presence of certain antigens/gycoproteins, complex (e.g., >three) chromosomal abnormalities, and presence of a monosomal karotype (National Comprehensive Cancer Network Guidelines™ [NCCN Guidelines™], 2014; NCI, 2014; National Cancer Institute [NCI], 2013b).

Successful treatment of acute myelogenous leukemia (AML) is divided into two major phases: induction-to attain remission and postremission consolidation/intensification-to maintain remission. Postremission therapy is always indicated in therapy that is planned with curative intent. Current approaches to postremission therapy include allogeneic or autologous hematopoietic stem-cell transplantation (HSCT) with high-dose chemotherapy or chemoradiation therapy (NCI, 2014).

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSC transplantation (HSCT) can be either autologous (using the patient'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.

Contraindications to HSCT
The presence of any significant co-morbid conditions that would significantly compromise clinical care and chances of survival is a contraindication to transplant. Greater age is associated with a higher incidence of post-transplantation complications; therefore, many centers restrict myeloablative allogeneic transplantation to patients age 55 or younger. 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

Myeloablative Allogeneic HSCT: Allogeneic HSCT results in the lowest incidence of leukemic relapse, which has led to the concept of a graft-versus-leukemia effect National Cancer Institute ([NCI], 2014). Disease-free survival (DFS) rates using allogeneic transplantation in first complete remission range from 45% to 60%. Although allogeneic HSCT provides the most potent anti-leukemia effect of any post remission therapy in acute myelogenous leukemia (AML), use of allogeneic HSCT for this indication results in transplant-related morbidity and mortality rates of 20%–40%, even with the use of an HLA-matched sibling donor (NCI, 2014).

If an HLA-matched sibling donor is available allogeneic HSCT is the preferred therapy for most individuals up to age 60 years who present with intermediate-risk karotypes or high-risk cytogenetics (NCI, 2014). The NCI also suggests that allogeneic transplantation may be considered in individuals with AML arising from myelodysplasia or secondary to previous cytotoxic chemotherapy if their overall performance status is adequate.

Individuals at high risk of relapse are unlikely to be cured with consolidation chemotherapy, and allogeneic HSCT allows the best chance for cure (NCI, 2014; NCI, 2013b). Patients who are treated with allogeneic HSCT have a significantly better survival rate compared to patients who are treated with other therapies (Giles, 2005). Allogeneic HSCT with an HLA-matched donor in early first relapse or in second complete remission provides a DFS rate of approximately 30% (NCI, 2014).

Despite second remission induction in over one-half of children with AML treated with drugs similar to drugs used in initial induction therapy, the prognosis for a child with recurrent or progressive AML is generally poor (NCI, 2013b). The selection of further treatment following the achievement of a second remission depends on prior treatment as well as individual considerations. Consolidation chemotherapy followed by HSCT is conventionally recommended, though there are no controlled prospective data regarding the contribution of

additional courses of therapy once a second complete remission is obtained. Unrelated donor hematopoietic stem-cell transplantation (HSCT) has been reported to result in five-year probabilities of leukemia-free survival of 45%, 20%, and 12% for patients with AML transplanted in second complete remission, overt relapse, and primary induction failure, respectively. The optimal type of preparative transplant regimen and source of donor cells has not been determined; alternative donor sources, including haploidentical donors, are being studied (NCI, 2013a)

Literature Review for Myeloablative HSCT
Several randomized controlled trials, meta-analyses and retrospective reviews have demonstrated relapse (RFS)-, disease-free (DFS), and overall (OS) survival benefit with the use of myeloablative allogeneic HSCT in first complete remission for individuals with poor- and intermediate risk AML. No improvement was noted for individuals with good-risk disease (Stelljes, 2011; Koreth, 2009; Fagioli, 2008; Gassas, 2008; Gorin, 2008; Cornelisson, 2007; Flynn, 2007; Bleakley, 2002).

Prospective trials of transplantation in children with AML suggest that 60% to 70% of children with five of six and six of six human leukocyte antigen (HLA)-matched donors who undergo allogeneic HSCT during first remission experience long-term remissions with reduced risk of relapse, improved DFS, and OS compared with intensive chemotherapy (National Cancer Institute [NCI], 2013b; Bleakley, 2002). Autologous HSCT studies were too heterogeneous to allow any generalized conclusions. An analysis of allogeneic and autologous HSCT performed for children with relapsed or refractory disease utilizing multiple donor types, conditioning regimens and graft-versus-host disease prophylaxis demonstrated no significant differences between the OS or event-free survival rates between the allogeneic and autologous groups (p=1.00 and p=.81, respectively) (Dvorak, 2008).

Relapse After Prior Allogeneic Transplant: A second myeloablative allogeneic HSCT has been proposed for individuals with AML who have undergone allogeneic HSCT and subsequently have disease relapse or progression. Hosing et al. (2005) evaluated outcomes from 72 patients with AML who were in disease relapse at the time of a second HSCT. Treatment-related mortality (TRM) was 36%. Patients who had relapsed or progressed more than one year after the first transplant had significantly better outcomes compared to patients who relapsed or progressed within one year. Patients with low leukemia burden (i.e., no peripheral blood blasts and ≤ 5% bone marrow blasts) at the time of the second HSCT had a five-year overall survival rate of 25%, compared to those with a high disease burden who had a five-year survival rate of 12%.

Summary for Myeloablative Allogeneic HSCT: According to the NCI (2014; NCI, 2013a), myeloablative allogeneic HSCT provides the most potent anti-leukemic effect of any post-remission therapy. It is considered an acceptable therapy for the treatment of selected adults and children with AML.

Non-Myeloablative Allogeneic HSCT: Myeloablative allogeneic HSCT results in unacceptable TRM for many patients, both due to the toxicity of the myeloablative regimen used as conditioning and the high incidence and severity of graft-versus host disease (GVHD) (Baron, 2007; Aoudjhane, 2005). Non-myeloablative or reduced-intensity allogeneic HSCT has been proposed to expand the populations of individuals who are eligible for HSCT.

Literature Review for Non-Myeloablative HSCT: Outcomes of several prospective clinical trials suggest reduced treatment-related toxicity, although relapse rate is higher in some studies. In other studies data suggests the type of conditioning had no impact on outcomes (Lioure, 2012; Baron, 2007; Grigg, 2007; Martino, 2007, Oran, 2007; Alyea, 2006). In a recent RCT by Lioure et al. (2012), the incidence of grade II-IV acute graft-versus-host disease was 51.9% and 11.3% (p<.0001),respectively, for myeloablative and reduced-intensity HSCT. Chronic GVHD rates were 45.8% and 41.7%, respectively, for myeloablative and reduced-intensity HSCT. OS was 63.4% and 65.8%, respectively, for myeloablative, and reduced-intensity HSCT.

Summary for Non-Myeloablative Allogeneic HSCT: Although clinical trial data are limited, non-myeloablative or reduced-intensity conditioning permits the use of allogeneic HSCT for a subset of individuals who may be unable to tolerate the toxic effects of myeloablative chemotherapy prior to allogeneic HSCT.

Autologous HSCT: According to the NCI (2013a), autologous HSCT is a reasonable treatment option for patients in second complete remission (CR), offering disease-free survival (DFS) that may be comparable to autografting in first CR (2013a). Treatment-related mortality (TRM) ranges from 10% to 20%.

Literature Review for Autologous Hematopoietic Stem-Cell Transplantation (HSCT): Several prospective studies have demonstrated no benefit in overall survival (OS) with the use of autologous HSCT compared with standard postremission chemotherapy in first complete remission (CR); however, disease-free survival (DFS) rates of 35%–50% have been noted.

Guieze et al. (2012) reported that autologous HSCT and allogeneic HSCT had similar outcomes compared with chemotherapy for patients with normal karyotype AML and adverse molecular features with leukemia-free- and overall survival rates. Autologous HSCT could represent a feasible alternative for treatment.

Thomas et al. (2007) reported the results of a prospective study including 757 patients with de novo previously untreated acute myelogenous leukemia (AML), or secondary AML. Ultimately, 35 patients received autologous HSCT after consolidation with high-dose chemotherapy HSCT. Three-year DFS and OS rates were 28% and 39%, respectively, for the transplanted patients. The three-year relapse incidence was 57%. Data suggest that intensification of chemotherapy using autologous HSCT did not improve overall health outcomes in this subset of individuals with AML.

Ravindranath et al. (2005) performed a retrospective review of the results of a total of 1823 children with AML enrolled in four consecutive Pediatric Oncology Group (POG) clinical trials. Of these, POG 8821 compared the efficacy of autologous HSCT with that of intensive consolidation chemotherapy. Intent-to-treat analysis revealed similar five-year event-free survival (EFS) estimates for the autologous HSCT (36%) and intensive chemotherapy (35%) groups. There was a high rate of treatment-related mortality in the autologous HSCT group.

Thomas et al. (2005) retrospectively reviewed the outcomes of 262 patients with relapsing and refractory leukemia achieving complete remission (CR). Transplantation was one of three favorable prognostic factors correlated with EFS: Three-year EFS rates were 68% versus 23% for autologous and allogeneic HSCT, respectively. Three-year probabilities of transplant-related mortality (TRM) were 11% and 47%, respectively, for autologous and allogeneic HSCT, respectively. In multivariate analysis, outcomes with autologous HSCT were significantly better than with allogeneic HSCT ($p<0.01$) or chemotherapy ($p=0.001$). Outcomes from allogeneic HSCT were not significantly different than those reported for standard-dose chemotherapy.

Two meta-analyses evaluated the outcomes of autologous HSCT versus chemotherapy in six studies of adult patients with AML in CR1. Patients receiving autologous HSCT had better EFS in both studies; however, there was no difference in OS. The studies did not address the effect in the high-risk population (Levi, 2004; Nathan, 2004).

Summary for Autologous HSCT: Overall, autologous HSCT appears to be inferior to allogeneic HSCT for the treatment of adults and children with acute myelogenous leukemia (AML). Although OS may not be improved with autologous HSCT, it may provide benefit to high-risk patients who have limited options because they lack a matched donor or cannot tolerate the conditioning therapy required for allogeneic HSCT. This therapy has the support of professional societies including the National Cancer Institute ([NCI], 2013a), which notes autologous HSCT may be an acceptable treatment option for individuals in second complete remission.

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

Professional Societies/Organizations
National Cancer Institute (NCI): Regarding HSCT for adults with AML the NCI (2014) notes:

- Current approaches to postremission therapy include high-dose chemotherapy or chemoradiation therapy with autologous bone marrow rescue, and high-dose marrow-ablative therapy with allogeneic bone marrow rescue.
- For AML in remission, allogeneic bone marrow transplantation results in the lowest incidence of leukemic relapse even when compared with bone marrow from an identical twin (syngeneic transplant).
- Transplantation should be offered to AML patients in first complete remission (CR1) in the setting of poor-risk cytogenetics and should not be offered to patients in CR1 with good-risk cytogenetics.

- Allogeneic HSCT can salvage some patients whose disease fails to go into remission with intensive chemotherapy (i.e., primary refractory leukemia).
- Autologous bone marrow transplantation is an option for patients in second complete remission.
- For adults with AML arising from myelodysplasia or secondary to previous cytotoxic chemotherapy may be treated primarily with allogeneic bone marrow transplantation if their overall performance status is adequate.

In children with AML the NCI (2013b) notes:

- Postremission therapy may consist of varying numbers of courses of intensive chemotherapy and/or allogeneic hematopoietic stem cell transplantation (HSCT).
- Matched family-donor hematopoietic stem-cell transplantation (HSCT) is an option only after first relapse and the achievement of a second complete remission.
- High-risk patients will be offered transplantation in first remission with the most appropriate available donor. Patients in the low-risk group will only be offered transplantation in second complete remission.
- There is evidence suggesting an advantage for allogeneic HSCT in patients in complete remission with intermediate-risk characteristics

The National Cancer Institute (NCI, 2013a) also notes ""In certain cases in which no suitable donor is found or an immediate transplant is considered crucial, a haploidentical transplant utilizing large doses of stem cells may be considered. For T-cell-depleted CD34-selected haploidentical transplants in which a parent is the donor, patients receiving maternal stem cells may have a better outcome than those who receive paternal stem cells."

The National Comprehensive Cancer Network™ (NCCN™): The NCCN publishes guidelines for the treatment of adults only. Clinical Practice Guidelines in Oncology for Acute Myelogenous Leukemia ([AML], 2014) suggests that age 60 years is considered a therapeutic divergence point for induction therapy recommendations. Regarding HSCT, the Guideline notes:

- For adults < 60 years of age, post induction therapy:
  - Allogeneic HSCT may be considered if a matched sibling or alternative donor has been identified.
- For adults < 60 years of age, post remission or consolidation therapy
  - Strategies include autologous hematopoietic stem-cell transplantation (HSCT) or allogeneic HSCT from matched sibling or unrelated donor
  - Transplant-based options afford a lesser risk of relapse and a somewhat higher disease-free survival as consolidation for an individual with intermediate-risk cytogenetics
  - Allogeneic sibling HSCT or human leukocyte antigen (HLA)-matched unrelated donors (including cord blood) or clinical trial is endorsed as consolidation for an individual with poor-risk cytogenetics or molecular abnormalities or with therapy-related AML or prior myelodysplasia. Another option is autologous HSCT if no allogeneic transplant option is available.
  - For individuals with better-risk cytogenetics an autologous HSCT is the preferred HSCT option. Allogeneic HSCT may be better reserved as salvage therapy or for those with C-KIT mutations.
- For adults <60 years of age, post–remission and salvage therapy:
  - For an individual who has experienced a relapse, salvage chemotherapy follows by allogeneic HSCT can be considered if the relapse is detected when the tumor burden is low and there is a previously identified sibling or unrelated donor. Transplant should only be considered if remission has been achieved or in the context of a clinical trial
- For adults ≥ 60 years old, post-induction therapy:
  - The role of myeloablative allogeneic HSCT is limited due to significant comorbidities; reduced intensity allogeneic HSCT as consolidation therapy may be considered.
  - Reduced intensity allogeneic HSCT is considered an additional option for the following indications: (1) as a post-remission therapy for those achieving a complete response to induction therapy (2) for treatment of induction failure only in an individual with low volume disease
- For adults ≥60 years old, post-remission and salvage therapy:
  - Salvage chemotherapy followed by matched sibling or alternate donor HSCT may be considered if the individual has achieved remission or in the context of a clinical trial

American Society for Blood and Marrow Transplantation (ASBMT): The ASBMT (2007) published a policy statement regarding treatment guidelines for children with acute myelogenous leukemia (AML) which notes:

- Autologous hematopoietic stem-cell transplantation (HSCT) and chemotherapy in the first complete remission (CR1) are equivalent in outcomes. The lack of data on quality of life, secondary malignancies, and other late effects of treatment prevent a recommendation of one treatment over the other.
- Allogeneic HSCT is recommended in CR1.
- The expert panel acknowledged a lack of evidence comparing matched related allogeneic donors (MRD) versus chemotherapy in second complete remission (CR2). The panel recommends the use of any suitable MRD if one is available. Use of a matched unrelated donor (MUD) or other alternative donor SCT is recommended in the context of a clinical trial.
- In CR2, the consensus recommends using any suitable MRD or MUD over autologous HSCT
- MRD allogeneic SCT is preferred in the first or second complete remission.

In 2008 the ASBMT published a policy statement regarding the role of cytotoxic therapy with HSCT for AML in adults which notes:

- There is no significant advantage of autologous HSCT over chemotherapy.
- There is a survival advantage for allogeneic HSCT versus chemotherapy for patients under age 55 with high risk cytogenetics.
- There is insufficient evidence to routinely recommend allogeneic HSCT for patients with intermediate cytogenetics, although this is a reasonable strategy.
- There is insufficient data to make a recommendation for the use of myeloablative regimens for patients over age 55.
- There is insufficient data to make a recommendation for reduced intensity conditioning (RIC) allogeneic HSCT versus chemotherapy.
- For patients in second complete remission, allogeneic HSCT is recommended if there is an available donor; otherwise an autologous HSCT is recommended.
- There are insufficient data to make a recommendation for tandem versus single autologous HSCT.
- Allogeneic SCT with a matched related donor is recommended if available; a matched unrelated donor HSCT using reduced intensity conditioning may provide equivalent outcomes.

National Marrow Donor Program (NMDP)/ASBMT: In development with the ASBMT, the NMDP (2012) lists the following as recommended timing for transplant consultation for AML: high-risk AML, including antecedent hematological disease (e.g., myelodysplasia (MDS)), treatment-related leukemia, and induction failure: CR1 with poor-risk cytogenetics or molecular markers, AML with relapse, and CR2 and beyond.

Use Outside of the US

National Institute of Health Research/Health Technology Assessment Programme (UK): Ashfaq et al. (2010) published a technology assessment of the clinical effectiveness and cost-effectiveness of stem-cell transplantation in the treatment of acute leukemia. The authors concluded “Bearing in mind the limitations, the existing evidence suggests that sibling donor allogeneic stem cell transplantation may be more effective than chemotherapy in adult AML (except in good-risk patients) in CR1, childhood AML in CR1, and adult acute lymphocytic leukemia in CR1. Autologous stem-cell transplantation is equal to or less effective than chemotherapy.”

Summary

Randomized controlled and prospective clinical trial evidence in the published peer-reviewed scientific literature supports the safety and effectiveness of myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) in carefully selected individuals with acute myelogenous leukemia (AML). Non-myeloablative allogeneic HSCT is an acceptable treatment option for individuals who meet criteria for allogeneic HSCT but for whom myeloablative therapy is contraindicated. Although data do not demonstrate improved overall survival with autologous HSCT, disease-free survival is improved. Additionally there is professional society support for subsets of individuals. At present, the role of tandem (sequential) transplantation has not been established for the treatment of individuals with AML.

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

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