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Hematopoietic Cell Transplantation (HCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information)

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Related Policies (if applicable)
703.001: Organ and Tissue Transplantation (General Donor and Recipient Information)

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

NOTE 1: See also SUR703.001, Organ and Tissue Transplantation (General Donor and Recipient Information).

NOTE 2: For policy coverage information on hematopoietic cell transplantation (HCT) for specific malignant or nonmalignant conditions, please refer to the specific Medical Policy.

Collection and Storage of Hematopoietic Cells
Stem cells, using bone marrow or peripheral blood, for **autologous** reinfusion or **allogeneic** infusion or transplantation following a chemotherapy/preparative regimen (high-dose, myeloablative or nonmyeloablative) **may be considered medically necessary** if the recipient has a condition or disorder for which the planned transplant is considered medically necessary and has met the transplant selection criteria; refer to the appropriate individual transplant policy for description and coverage information.

Umbilical cord blood (UCB) hematopoietic cell transplantation, following a chemotherapy/preparative regimen (high-dose, myeloablative or nonmyeloablative), **may be considered medically necessary** in individuals who have met the transplant selection criteria, and who have an appropriate indication for **allogeneic** HCT, but who do not have a hematopoietic stem cell donor; refer to the appropriate individual transplant policy for description and coverage information.

Collection and storage of UCB stem cells from a newborn **may be considered medically necessary** when an **allogeneic** HCT is imminent (less than one year) in an identified recipient, such as a sibling, with a diagnosis that is consistent with the possible need for allogeneic transplant.

Prophylactic collection and storage of UCB stem cells from a newborn AND/OR speculative collection and storage of stem cells from donor-recipient (**autologous**) **or** from related or unrelated donor (**allogeneic**) **is considered not medically necessary** when proposed for potential and unspecified future use, such as but not limited to a potential and unspecified future use as an:

- **Autologous** HCT in the original donor; OR
- **Allogeneic** HCT in a related or unrelated recipient.

Stem Cell Purging

Stem cell purging is an integral part of the **autologous** stem cell preparation after harvesting and **is not eligible for additional reimbursement** beyond the standard stem cell donation preparation prior to recipient infusion.

Stem cell purging as part of the **allogeneic** stem cell preparation after harvesting **is considered not medically necessary** as an **allogeneic** stem cell donation should be cancer free prior to recipient infusion.

Donor Lymphocyte Infusion (DLI) or Hematopoietic Progenitor Cell (HPC) Stem Cell Boost

DLI or HPC stem cell boost **may be considered medically necessary** following **allogeneic** HCT that was originally considered medically necessary for the treatment of hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse (includes T-cell depleted grafts or nonmyeloablative/reduced intensity conditioning), or to convert a patient from mixed to full donor chimerism.

DLI or HPC stem cell boost **are considered experimental, investigational and/or unproven** following **allogeneic** HCT that was originally considered experimental, investigational and/or unproven for the treatment of a hematologic malignancy.

DLI or HPC stem cell boost **are considered experimental, investigational and/or proven** as a treatment of nonhematologic malignancies following a prior **allogeneic** HCT.

DLI or HPC stem cell boost **are considered experimental, investigational and/or unproven** as a treatment of hematologic or nonhematologic malignancies following a prior **autologous** HCT.

Genetic modification of donor lymphocytes for infusion at any point following any HCT treatment **is considered experimental, investigational and/or unproven**.

Short Tandem Repeat (STR) Markers
Short tandem repeat (STR) markers **may be considered medically necessary** when used in pre- or post-HCT testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment for some hematological disorders.

Policy Guidelines

Charges for the acquisition of cord blood (CB) through a CB bank may be submitted as part of the hospital bill or claim. Cryopreservation processing and storage may be billed separately from other vendors.

Description

Human blood contains a remarkable variety of cells, each precisely tailored to its own vital function. Erythrocytes, or red blood cells, transport life-sustaining oxygen throughout the body. Tiny platelets stop bleeding by promoting clotting. White blood cells (e.g., lymphocytes, monocytes, and neutrophils) form the immune system that guards against attack by foreign tissue, viruses, and various other microorganisms.

All of these cells develop from master cells or blood cell progenitors, which are known as hematopoietic blood-forming or blood-parent stem cells (HSCs) and reside primarily in bone marrow. Injury to the stem cells, from chemotherapy, radiation, or disease, can cripple the immune and blood production systems.

Background
HSCs are the main ingredient in bone marrow stem cell transplantation (also known as hematopoietic cell transplant, transplantation, rescue or support; HCT). The HSCs in the transplanted marrow can reestablish the patient's blood-producing and immune systems, which have been devastated by leukemia, cancer, chemotherapy, radiation therapy, or unknown causes. The objective of all types of HCT is to provide the healthy stem cell population that will differentiate into blood cells to replace the deficient or pathologic cells of the host. Therefore, the purpose of HCT is to restore the stem cells after injury to normal function.

The most appropriate stem cell source for a particular patient depends upon his or her disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each patient must be balanced by the risks of graft failure, the reinfusion of defective or diseased cells in the autologous procedure, the risks of graft rejections and graft-

versus-host disease (GVHD) in allogeneic procedures. This becomes especially critical with the use of a mismatched or unrelated donor.

Steps Involved for a HCT:
1. Donor matching to the recipient,
2. Preparative conditioning or regimens for the recipient,
3. Harvesting stem cells from the donor,
4. Infusion or transplantation of stem cells to the recipient,
5. Engraftment and recovery by the recipient, and
6. Additional infusions to the recipient as needed.

Preparative Conditioning or Regimens for the Recipient

Conventional Preparative Conditioning (High-Dose Chemotherapy [HDC])*:*

The conventional "classical" practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning (RIC)*:*

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation

develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism. In this policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Harvesting Stem Cells from the Donor

Stem cells can be harvested from the donor's bone marrow prior to the recipient's marrow ablative therapy or from a donor's marrow after verifying the donor and recipient are well-matched with respect to human leukocyte antigens (HLAs). Those types of stem cells harvesting followed by infusion are:

- Autologous – Stem cells are harvested from an individual prior to any ablative therapy and infused back (reinfusion) into the same individual.
- Allogeneic – Stem cells from a healthy antigen compatible (histocompatible) donor are harvested and then infused into a different recipient.
- Syngeneic – Stem cells from a genetically identical bone marrow or peripheral stem cells harvested from an identical twin. Syngeneic bone marrow transplants are obviously limited by the rarity of identical twins.

Infusion of Stem Cells to the Recipient

Once the recipient has completed the preparative conditioning or regimen, the infusion of stem cells is accomplished through an intravenous line, similar to a blood transfusion, taking about 1 to 5 hours.

Hematopoietic Cell Transplantation Procedure

Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Additional Infusions or Boosts

Donor Lymphocyte Infusions (DLI):

DLI, also called donor lymphocyte or buffy-coat infusion/transfusion, is a type of therapy in which T-lymphocytes from the blood of a donor are given to a patient who has already received a HCT from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or

graft-versus-tumor effect due to recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells.

Timing of the use of DLI depends upon the disease indication and may be used in the setting of relapse after an allogeneic HCT, as a planned strategy to prevent disease relapse in the setting of T cell depleted grafts or nonmyeloablative conditioning regimens, or as a method to convert mixed to full donor chimerism.

The source of the DLI donor cells can be from a previously collected and cryopreserved reserve or can be freshly harvested, provided from the original stem cell donor. Collection of donor lymphocytes requires that the original donor undergo a leukapheresis procedure. This additional DLI, which is a form of adoptive immunotherapy, induces a graft-versus-tumor response, without the need for additional peripheral blood stem cell harvest from the donor, or further chemotherapy for the recipient. These patients do not receive immunosuppressive medication.

DLI is used in nearly all hematologic malignancies for which allogeneic HCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma and Hodgkin and non-Hodgkin lymphoma.

Hematopoietic Progenitor Cell (HPC) or Stem Cell Boost:
Much like DLI, HPC boosts or stem cell boosts/boost infusions are given as a post-allogeneic HCT for engraftment failure. This may be a result of inadequate stem cell numbers (such as a single UCB unit), infections, GVHD, graft failure including late rejection, and immunological mediated processes, such as poorly matched donor/recipient, HCT with depleted T-cells, refractory pure red cell aplasia caused by remaining recipient cells producing anti-erythrocyte antibodies or DLI induced pancytopenia. This post transplantation condition is life-threatening and uncommon but can be overcome by an additional infusion of HSCs, if available. Additional chemotherapy or total body irradiation is not given prior to the stem cell boost of donor cells; and this is not considered a second or tandem transplantation.

Tandem Transplantation (Including Triple Transplantation)
Tandem transplants usually are defined as the planned administration of two successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic stem cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use nonmyeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.

Functional Status of Cancer Patients
Oncologists have identified that the functional status of the patient can be correlated with the outcome of the `underlying disease. The following Karnofsky Performance Status Scale (Table 1) has been the most widely used measure of the functional status of cancer patients. (1)

Table 1. Karnofsky Performance Status (Scale)

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity, no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do work	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed
60	Requires occasional assistance from others, but able to care for most needs	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing
30	Severely disabled, hospitalization indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

Additional Definitions

Listed below are several definitions, not included in the above Description:

- Complete remission or response (CR) is the disappearance or absence of the signs and symptoms of the disease.
- Malignancy refers to a harmful uncontrolled growth that can spread throughout the body and eventually lead to death.
- Monotherapy refers to a therapy that uses only one drug.
- Non-malignancy refers to a benign growth or condition, such as dysplasias.
- Plateau indicates stable values or response for at least three months.
- Relapsed is defined as tumor recurrence after a prior CR.
- The term "salvage therapy" describes chemotherapy given to patients who have:
    1. Failed to achieve CR after initial treatment for newly diagnosed malignancy; or
    2. Relapsed after an initial CR.
- Short tandem repeat (STR) markers may be performed prior to stem cell reinfusion or transplantation to determine the difference between donor and recipient DNA patterns. This information will be used post stem cell reinfusion or transplantation to assess the

status of donor cell engraftment. Additionally, STR may be used in genetic genealogy or ancestry research, paternity testing, forensic or criminal DNA mapping or profiling and preimplantation genetic testing.

- Stem cell purging is a technique to attempt removing any remaining tumor or cancer cells in the patient's autologous harvested stem cell donation from bone marrow or peripheral blood to minimize the chance that the malignancy will return. Purging is part of the stem cell process in preparation for infusion to the autologous donor-recipient minimizing tumor contamination.

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research (CBER), under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale

This medical policy was created in 1990 and has been updated periodically with searches of the PubMed database. The most recent literature review was performed through March 22, 2024.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Cord Blood as Source of Stem Cells for Stem Cell Transplant

A variety of malignant diseases and nonmalignant bone marrow disorders are treated with myeloablative therapy followed by infusion of the allogeneic stem and progenitor cells

collected from immunologically compatible donors, either family members or an unrelated donor identified through a bone marrow donor bank. In some cases, a suitable donor is not found.

Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells capable of restoring hematopoietic function after myeloablation. This cord blood has been used as an alternative source of allogeneic stem cells. Cord blood is readily available and is thought to be antigenically "naive," thus potentially minimizing the incidence of graft-versus-host disease (GVHD) and permitting the broader use of unrelated cord blood transplants. Unrelated donors are typically typed at low resolution for human leukocyte antigen (HLA)-A and -B and at high resolution only for HLA DR; HLA matching at 4 of 6 loci is considered acceptable. Under this matching protocol, an acceptable donor can be identified for almost any patient.

Several cord blood banks have been created in the U.S. and Europe. In addition to obtaining cord blood for specific related or unrelated patients, some cord blood banks collect and store neonate cord blood for some unspecified future use in the unlikely event that the child develops a condition that would require autologous transplantation. Also, some neonate cord blood is collected and stored for use by a sibling in whom an allogeneic transplant is anticipated due to a history of leukemia or other condition requiring an allogeneic transplant.

Standards and accreditation for cord blood banks are important for assisting transplant programs in knowing whether individual banks have quality control measures in place to address issues such as monitoring cell loss, change in potency, and prevention of product mix-up. (2) Two major organizations have created accreditation standards for cord blood banks in the U.S.: the American Association of Blood Banks and the International NetCord Foundation/Foundation for the Accreditation of Cellular Therapy. Both the American Association of Blood Banks and the International NetCord Foundation/Foundation for the Accreditation of Cellular Therapy have developed and implemented a program of voluntary inspection and accreditation for cord blood banking. The American Association of Blood Banks and the International NetCord Foundation/Foundation for the Accreditation of Cellular Therapy publish standards for cord blood banks that define the collection, testing, processing, storage, and release of cord blood products. (3)

Clinical Context and Therapy Purpose

The purpose of using placental and umbilical cord blood as a source of stem cells is to provide an alternative to or an improvement on existing donor sources in individuals with an appropriate indication for allogeneic stem cell transplant.

The question addressed in this medical policy is: Does the use of placental and umbilical cord blood as a source of stem cells for individuals with an indication for allogeneic stem cell transplantation result in an improvement in net health outcomes?

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with an appropriate indication for allogeneic stem cell transplant.

Interventions
The therapy being considered is placental or umbilical cord blood as a source of stem cells for allogeneic stem cell transplantation. Individuals with an appropriate indication for allogeneic stem cell transplant are managed by a transplant specialist in an inpatient clinical setting.

Comparators
Comparators of interest include stem cells from other donor sources.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, resource utilization, and treatment-related mortality.

The timing of follow-up is initially the first post-transplant year for successful engraftment and monitoring relevant outcomes. Follow-up is life-long for successful transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Related Allogeneic Cord Blood Transplant
The first cord blood transplant involved a child with Fanconi anemia; results were reported in 1989. (4) Subsequently, other cord transplants have been performed in matched siblings. The results of these transplants have demonstrated that cord blood contains sufficient numbers of hematopoietic stem and progenitor cells to reconstitute pediatric patients. Lower incidence of acute and chronic graft-versus-host disease (GVHD) have been observed when cord blood, compared with bone marrow, was used as the source of donor cells. (5) This led to the idea that cord blood could be banked and used as a source of unrelated donor cells, possibly without full human leukocyte antigen (HLA) matching. (6)

Unrelated Allogeneic Cord Blood Transplant
The first prospective evaluation of unrelated cord blood transplant was the Cord Blood Transplantation study, published in 2005. The Cord Blood Transplantation study was designed to examine the safety of unrelated cord blood transplantation in infants, children, and adults.

Two-year event-free survival was 55% in children with high-risk malignancies, (7) and 78% in children with nonmalignant conditions. (8) Across all groups, the cumulative incidence of engraftment by day 42 was 80%. Engraftment and survival were adversely affected by lower cell doses, pretransplant cytomegalovirus (CMV) seropositivity in the recipient, non-European ancestry, and higher HLA mismatching. This slower engraftment leads to longer hospitalizations and greater utilization of medical resources. (9) In the Cord Blood Transplantation study, outcomes in adults were inferior to the outcomes achieved in children.

Zhang et al. (2012) published a meta-analysis of studies comparing unrelated donor cord blood transplantation to unrelated donor bone marrow transplantation in patients with acute leukemia. (10). Reviewers identified 7 studies (total n=3389 patients). Pooled rates of engraftment failure (n=5 studies) were 18% (127/694 patients) in the cord blood transplant group and 6% (57/951 patients) in bone marrow transplant groups. The rate of engraftment graft failure was significantly higher in cord blood transplantation recipients ($p<0.001$). However, rates of acute GVHD were significantly lower in the cord blood transplant group. Pooled event rates of GVHD (n=7 studies) were 34% (397/1179 patients) in the cord blood group and 44% (953/2189 patients) in the bone marrow group ($p<0.001$). Relapse rates, reported in all studies, did not differ significantly between groups. Several survival outcomes including overall survival, leukemia-free survival, and nonrelapse mortality favored the bone marrow transplant group.

Also, numerous retrospective and registry studies have generally found that unrelated cord blood transplantation is effective in both children and adults with hematologic malignancies and in children with a variety of nonmalignant conditions. (11-13) For example, a study by Liu et al. (2014) compared outcomes after unrelated donor cord blood transplantation versus matched-sibling donor peripheral blood transplantation. (13) The study included patients age 16 years or older who had hematologic malignancies. Seventy patients received unrelated cord blood, and 115 patients received HLA-identical peripheral blood stem cells, alone or in combination with bone marrow. Primary engraftment rates were similar in the 2 groups, 97% in the cord blood group and 100% in the peripheral blood stem cell group. Rates of most outcomes, including grades III to IV acute GVHD and 3-year disease-free survival were also similar between groups. However, the rate of chronic GVHD was lower in the unrelated donor cord blood group. Specifically, limited or extensive chronic GVHD occurred in 12 (21%) of 58 evaluable patients in the cord blood group and 46 (42%) of 109 evaluable patients in the peripheral blood stem cell group ($p=0.005$).

Fuchs et al. (2020) reported on outcomes of 2 parallel phase 2 trials comparing unrelated umbilical cord blood transplantation versus haploidentical bone marrow transplantation in 368 patients aged 18 to 70 years old. (14) The 2-year progression-free survival (the primary endpoint) was 35% (95% confidence interval [CI], 28% to 42%) after cord blood transplants and 41% (95% CI, 34% to 48%) after haploidentical bone marrow transplants ($p=0.41$). The 2-year non-relapse mortality was 18% (95% CI, 13% to 24%) with cord blood transplant versus 11% (95% CI, 6% to 16%) with haploidentical transplants ($p=0.04$), resulting in a 2-year OS of 46%

(95% CI, 38% to 53%) with cord blood transplant versus 57% (95% CI, 49% to 64%) with haploidentical bone marrow transplants (p=0.04).

Haplo-Cord Blood Transplantation

Haplo-cord transplants involve a combination of donated cord blood stem cells and half-matched (haploidentical) cells from a related donor.

Mo et al. (2016) reported on outcomes after UCB and haploidentical hematopoietic cell transplantation (haplo-HCT) in 129 children younger than 14 years old. (15) The 2-year probability of OS was 82% (95% confidence interval [CI], 72.2% to 91.8%) in the haplo-HCT group and 69.9% (95% CI, 58.0% to 81.2%) in the cord blood group. The difference in OS between groups was not statistically significant (p=0.07). The 2-year incidence of relapse was also similar in the 2 groups: 16% (95% CI, 6.1% to 26.1%) in the haplo-HCT group and 24.1% (95% CI, 12.5% to 37.5%) in the cord blood group (p=0.17).

Hsu et al. (2018) reported on patients with lymphoma or chronic lymphoblastic leukemia who underwent haplo-cord allogeneic stem cell transplantation. (16) Forty-two patients treated between 2007 and 2016 were included in the analysis. After a median survivor follow-up of 42 months, the median 3-year GVHD relapse-free survival, progression-free survival, and OS were 53% (95% CI: 36-68%), 62% (95% CI: 44-75%), and 65% (95% CI: 48-78%), respectively. The cumulative incidence of relapse was 12% at 100 days and 19.5% at 1 year.

Poonsombudlert et al. (2019) performed a meta-analysis of 7 studies (N=3,434) comparing haploidentical transplant utilizing post-transplant cyclophosphamide versus umbilical cord transplant in patients without a matched relative. (17) Compared with umbilical cord transplant, haploidentical transplant utilizing cyclophosphamide was associated with a decreased risk of acute GVHD (odds ratio [OR], 0.78; 95% CI, 0.67 to 0.92) and relapse (OR, 0.74; 95% CI, 0.57 to 0.97) and an improved rate of chronic GVHD (OR, 1.41; 95% CI, 1.02 to 1.95) and OS (OR, 1.77; 95% CI, 1.1 to 2.87).

Li et al. (2020) performed a meta-analysis of 7 studies in adult and pediatric patients with hematological malignancies (N=2,422) undergoing umbilical cord blood transplantation or haploidentical transplantation. (18) The results revealed a similar incidence of chronic GVHD and disease-free survival at 2 years between the 2 types of transplant in children. In adults, grade II to IV acute GVHD occurred at a higher rate with umbilical cord blood transplantation versus haploidentical transplantation (relative risk [RR], 1.17; 95% CI, 1.02 to 1.34; p=0.02). Rates of grade III to IV acute GVHD, chronic GVHD, relapse, nonrelapse mortality, and disease-free survival at 2 years were similar between the 2 transplant types in adults.

Wu et al. (2020) performed a meta-analysis of 12 studies (N=2,793) comparing haploidentical HCT versus umbilical cord blood transplantation for hematologic malignancies. (19) Compared with umbilical cord blood transplantation, HCT improved OS (OR, 0.74; 95% CI, 0.68 to 0.80), progression-free survival (OR, 0.77; 95% CI, 0.72 to 0.83), non-relapse mortality (OR, 0.72, 95%

CI, 0.64 to 0.80), and acute GVHD (OR, 0.87; 95% CI, 0.77 to 0.98) but also increased the risk for chronic GVHD (OR, 1.40; 95% CI, 1.22 to 1.62).

Double Unit Cord Blood Transplantation

Transplantation of 2 UCB units (or double-unit transplants) has been evaluated as a strategy to overcome cell dose limitations with 1 cord blood unit in older and heavier patients. Initial experience at a university showed that using 2 units of cord blood for a single transplant in adults improved rates of engraftment and OS. (20) Although cell doses are higher with double-unit transplants, studies published to date have found that survival rates are similar to transplants using single-cord blood units, and there is some suggestion of higher rates of GVHD (see Tables 2 and 2). (21)

Table 2. Summary of Key Trial Characteristics

Author	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Wagner et al. (2014) (21)		1		Patients (age range, 1-21 y) who had high-risk acute leukemia, chronic myeloid leukemia, or myelodysplastic syndrome for whom there were 2 HLA-matched cord blood units available	2 units	1 unit

HLA: human leukocyte antigen; y: year(s).

Table 3. Summary of Key Trial Results (N=224)

Study (Year)	1-Year OS	1-Year DFS	Acute GVHD	Chronic GVHD
Wagner et al. (2014) (21)				
Single unit (95% CI), %	73 (63 to 80)	70 (60 to 77)	13 (7 to 20)	30 (22 to 39)
Double unit (95% CI), %	65 (56 to 74)	64 (54 to 72)	23 (15 to 31)	32 (23 to 40)
p	0.17	0.011	0.02	0.51

CI: confidence interval; DFS: disease-free survival; GVHD: graft-versus-host disease; OS: overall survival.

Results of observational studies are similar to those of the Wagner et al. (2014) RCT (see Tables 4 and 5). In a study by Scaradavou et al. (2013) there was a significantly higher risk of acute GVHD (grade II-IV) in recipients of double-cord blood units treated during the first several years of observation. (22) In the later period (2004-2009), rates of acute GVHD (grade II-IV) did not differ significantly between single- and double-units of cord blood. An analysis by Baron et al. (2017) found no significant differences between single- and double-cord blood transplantation for relapse or nonrelapse mortality, with a trend (p=0.08) toward a higher incidence of GVHD with double units. (23)

Table 4. Summary of Key Observational Study Characteristics

Author (Year)	Study Type	Dates	Participants	Treatment		Follow Up
				Arm 1	**Arm 2**	
Scaradavou et al. (2013) (22)	Comparative cohort	2002-2004 2004-2009		Single unit	Double unit	
Baron et al. (2017) (23)	Registry	2004-2014	Adults with first CBT for AML or ALL	Single unit	Double unit	2 years

ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CBT: cord blood transplantation.

Table 5. Summary of Key Observational Study Results

Study (Year)	N	Relapse Mortality	Nonrelapse Mortality	Acute GVHD (95% CI)	
				2002-2004	**2004-2009**
Scaradavou et al. (2013) (22)					
Single unit					
Double unit					
HR (95% CI)				6.14 (2.54 to 14.87)	1.69 (0.68 to 4.18)
p				<0.001	0.30
				2004-2014	
Baron et al. (2017) (23)					
Single unit	172				
Double unit	362			28%	
HR (95% CI)		0.9 (0.6 to 1.3)	0.8 (0.5 to 1.2)	36%	
p		0.5	0.3	0.08	

CI: confidence interval; GVHD: graft-versus-host disease; HR: hazard ratio

Section Summary: Cord Blood as Source of Stem Cells for Stem Cell Transplant

A number of observational studies and a meta-analyses of observational studies have compared outcomes after cord blood transplantation with stem cells from a different source. One meta-analysis found similar survival outcomes and lower GVHD after cord blood transplantation than bone marrow transplantation, but a recent RCT showed improved survival outcomes with haploidentical bone marrow transplantation over umbilical cord blood transplantation. Also, an RCT has compared single- and double-unit cord blood transplantation and found similar outcomes.

Prophylactic Collection and Storage of Cord Blood

Clinical Context and Therapy Purpose

The purpose of prophylactic collection and storage of placental or umbilical cord blood stem cells is to provide an alternative donor source for individuals without or with an unspecified potential future need for stem cell transplant.

The question addressed in this medical policy is: Does the prophylactic collection and storage of placental and umbilical cord blood stem cells to provide an alternative donor source for individuals without or with an unspecified potential future need for stem cell transplantation improve net health outcomes.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals without or with an unspecified potential future need for stem cell transplant.

Interventions
The test being considered is prophylactic collection and storage of placental or umbilical cord blood stem cells.

The collection and preservation of placental or umbilical cord for future use is carried out at the time of labor and delivery and is carried out by commercial service providers.

Comparators
Comparators of interest include usual care without prophylactic storage of cord blood.

Outcomes
The general outcomes of interest are OS, disease-specific survival, resource utilization, and treatment-related mortality.

The future use of stored stem cells is unknown and, thus, the follow-up time period to transplant is indeterminate.

No studies have compared outcomes after prophylactic collection and storage of cord blood from a neonate for individuals who have an unspecified future need for transplant to standard care without cord blood collection and storage.

Although blood banks are collecting and storing neonate cord blood for potential future use, data on the use of cord blood for autologous HCT are limited. A 2017 position paper from the American Academy of Pediatrics noted that there is no evidence of the safety or effectiveness of autologous cord blood transplantation for treatment of malignant neoplasms. (24) Also, a 2009 survey of pediatric hematologists noted few transplants have been performed using cord blood stored in the absences of a known indication. (25)

<u>Section Summary: Prophylactic Collection and Storage of Cord Blood</u>

There is a lack of published evidence comparing outcomes after prophylactic collection and storage of cord blood from a neonate for individuals who have an unspecified future need for transplant to standard care without cord blood collection and storage.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 6.

Table 6. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01728545	The Collection and Storage of Umbilical Cord Blood for Transplantation	250,000	Apr 2099
NCT00012545	Collection and Storage of Umbilical Cord Stem Cells for Treatment of Sickle Cell Disease	500	Not Reported

NCT: National Clinical Trial.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2017, a position statement on cord blood banking for potential future transplantation was published by the American Academy of Pediatrics. (24) The Academy recommended cord blood banking for public use, with a more limited role for private cord blood banking for families with a known fatal illness that could be rescued by cord blood transplant.

American College of Obstetricians and Gynecologists (ACOG)

In 2015, with an update in 2019, the American College of Obstetricians and Gynecologists published an opinion on UCB banking. (26) The statement discussed counseling patients on options for UCB banking, as well as the benefits and limitations of this practice.

The relevant recommendations included the following:

- "[UCB] collected from a neonate cannot be used to treat a genetic disease or malignancy in that same individual."
- "The routine collection and storage of [UCB] with a private cord blood bank is not supported by the available evidence."
- "Private [UCB] banking may be considered when there is knowledge of a family member with a medical condition (malignant or genetic) who could potentially benefit from cord blood transplantation."
- "Public [UCB] banking is the recommended method of obtaining [UBC] for use in transplantation, immune therapies, or other medically validated indications."
- "Umbilical cord blood collection should not compromise obstetric or neonatal care or alter routine practice for the timing of umbilical cord clamping."
- "The current indications for cord blood transplant are limited to select genetic, hematologic, and malignant disorders."

- "If a patient requests information about [UCB] banking, balanced and accurate information regarding the advantages and disadvantages of public and private [UCB] banking should be provided."

American Society for Blood and Marrow Transplantation (ASBMT)
In 2008, on behalf of the ASBMT, Ballen et al. published recommendations related to the banking of UCB (27):

- Public banking of cord blood is "encouraged".
- Storage of cord blood for autologous (i.e., personal) use "is not recommended".
- "Family member banking (collecting and storing cord blood for a family member) is recommended when there is a sibling with a disease that may be successfully treated with an allogeneic transplant. Family member banking on behalf of a parent with a disease that may be successfully treated with an allogeneic transplant is only recommended when there are shared HLA antigens between the parents."

American Society of Transplantation and Cellular Therapy
In 2020, the American Society of Transplantation and Cellular Therapy released an evidence-based review on hematopoietic cell transplantation for treating newly diagnosed adult acute myeloid leukemia. (28) The summary stated that a haploidentical related donor is preferred over UCB in the absence of a fully HLA-matched donor, but UCB unit transplantation is an option for centers with this expertise.

Summary of Evidence
For individuals who have an appropriate indication for allogeneic stem cell transplant who receive cord blood as a source of stem cells, the evidence includes a number of observational studies, a meta-analysis of observational studies, and randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, resource utilization, and treatment-related mortality. A meta-analysis of observational studies found similar survival outcomes and lower graft-versus-host disease (GVHD) after umbilical cord blood (UCB) transplantation than bone marrow transplantation, but a recent RCT showed improved survival outcomes with haploidentical bone marrow transplantation over umbilical cord blood transplantation. In another RCT, survival rates were similar after single- and double-unit UCB transplantation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have an unspecified potential future need for stem cell transplant who receive prophylactic collection and storage of UCB, the evidence includes no published studies. Relevant outcomes are overall survival, disease-specific survival, resource utilization, and treatment-related mortality. No evidence was identified on the safety or effectiveness of autologous UCB transplantation from prophylactically stored UCB for the treatment of malignant neoplasms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Stem Cell Purging

The value of stem cell purging, particularly for autologous HCT, is to improve the hematopoietic elements that are enriched to establish engraftment (positive selection) of progenitor cells or to remove contaminated cancerous cells prior to stem cell infusion (negative selection) back to the donor. (29) To purge contaminated cells for autologous donation, anti-cancer drugs may be given directly to the stem cells collected. (30) This process is an integral part of the stem cell preparation; however, the risk cancer cells return is not known. The most current method is not to purge prior to the transplantation, but administering a monoclonal antibody treatment following the transplantation, particularly for some leukemias and lymphomas, known as *in vivo purging*. Studies for drug preparations are still being performed to determine the best match of drug to cancer for *in vivo purging*. (30)

Numerous pre-clinical discussions were published and clinical trials performed during the 1990's through the early 2000's in autologous HCT treatments. (31-41) The conditions studied included acute lymphoblastic leukemia (ALL), acute myelogenous leukemia *(*AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplasia syndrome (MDS), multiple myeloma (MM), and non-Hodgkin lymphoma (NHL) (including follicular and mantle cell lymphoma). For patients undergoing autologous HCT, self-donations of progenitor cells are likely to be contaminated with the tumor cells, placing the patients at a higher risk of relapse. Elimination of those tumor cells will decrease the risk of relapse in those with advanced disease. However, this preparative purging step is included in overall HCT protocol/process to treat a specific condition. (41)

Studies on purging allogeneic donations are scant. The unrelated or related donor should be cancer-free prior to harvesting of progenitor cells. However, some cancer center protocols may include this step in their process to promote engraftment by cleaning the stem cells of any diseases that may promote relapse or appearance of an unexpected condition (e.g., human immunodeficiency virus [HIV]). (41)

Summary of Evidence

For individuals who have an appropriate indication for autologous hematopoietic cell transplantation (HCT), malignant cells are purged to prevent relapse. The evidence includes several clinical trials to assess overall survival, disease-specific survival, resource utilization, and treatment-related mortality. There are complex graft manipulations during the process following autologous harvesting in preparation of the autologous donation, achieving less risk of receiving malignant cells back to the individual. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals undergoing allogeneic HCT, the donor should be cancer-free prior to harvesting of progenitor cells. Studies on purging allogeneic donations are scant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Donor Lymphocyte Infusion (DLI) and Stem Cell Boost

DLI

Chronic Myelogenous Leukemia
DLI has been found to be most effective in CML, inducing a molecular complete remission (CR) in up to 80% of patients who relapse in chronic phase. Only a 12.5% to 33% response rate has been reported in patients in accelerated or blast phase. Response duration to DLI in patients with relapsed CML after HCT is long-standing in most patients.

Several large series have reported outcomes of patients with relapsed CML after receiving DLI. (42-45) These studies comprise more than 1000 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI. (46) The cell doses varied among patients, with some patients receiving multiple DLI infusions and others planned dose escalations. Despite these variations, a molecular CR was achieved in 77% of patients (405/527). OS at 3 or more years ranging from 53% to 95%, (47) was 64% at 5 years, and was 59% at 10 years after DLI in another series. (48)

The role of DLI in CML has changed as the use of tyrosine-kinase inhibitors has revolutionized the treatment of CML by keeping the disease under control instead of proceeding to HCT. However, for patients who develop resistance to the tyrosine-kinase inhibitors or are unable to tolerate the adverse effects, HCT and DLI may be a disease management option.

Acute Leukemias, Myelodysplasia, and Other Myeloproliferative Diseases
In a 2013 systematic review, El-Jurdi et al. evaluated 39 prospective and retrospective studies on DLI for relapse after HCT for lymphoid malignancies including ALL, CLL, MM, NHL, and Hodgkin lymphoma (HL). (49) No randomized controlled studies were identified. The studies were heterogeneous thus limiting interpretation of the review. Reported pooled proportions of CR (95% confidence interval [CI]) were 27% (16% to 40%) for ALL, 55% (15% to 92%) for CLL, 26% (19% to 33%) for multiple myeloma, 52% (33% to 71%) for NHL, and 37% (20% to 56%) for HL.

An observational study compared different treatments for 147 consecutive patients who relapsed after allogeneic HCT for myelodysplastic syndrome. (50) Sixty-two patients received HCT or DLI, 39 received cytoreductive treatment, and 46 were managed with palliative or supportive care. Two-year OS rates were 32%, 6%, and 2%, respectively ($p<.001$). In multivariate analysis, 4 factors adversely influenced 2-year OS rates: history of acute GVHD (hazard ratio [HR], 1.83; 95% CI, 1.26 to 2.67; $p=0.002$), relapse within 6 months (HR=2.69; 95% CI, 0.82 to 3.98; $p<0.001$), progression to acute myelogenous leukemia (HR=2.59; 95% CI, 1.75 to 3.83; $p<0.001$), and platelet count less than 50 g/L at relapse (HR=1.68; 95% CI, 1.15 to 2.44; $p=0.007$). HCT or DLI was an independent factor that favorably impacted OS (HR=0.40; 95% CI, 0.26 to 0.63; $p<0.001$).

Patriarca et al. (2020) conducted a retrospective multicenter study including pediatric and adult patients with acute leukemia (AL) who received DLIs after allogeneic HCT between January 1, 2010, and December 31, 2015, to determine the efficacy and toxicity of the immune treatment. (51) Two hundred fifty-two patients, median age 45.1 years (1.6–73.4), were enrolled from 34 Italian transplant centers. The underlying disease was AML in 180 cases (71%). Donors were

HLA identical or 1 locus mismatched sibling (40%), unrelated (40%), or haploidentical (20%). The first DLI was administered at a median time of 258 days (55–3,784) after HCT. The main indication for DLI was leukemia relapse (73%), followed by mixed chimerism (17%), and pre-emptive/prophylactic use (10%). Ninety-six patients (38%) received one single infusion, whereas 65 (26%), 42 (17%), and 49 patients (19%) received 2, 3, or ≥4 infusions, respectively, with a median of 31 days between two subsequent DLIs. Forty percent of evaluable patients received no treatment before the first DLI, whereas radiotherapy, conventional chemotherapy or targeted treatments were administered in 3, 39, and 18%, respectively. In informative patients, a few severe adverse events were reported: grade III–IV GVHD (3%), grade III–IV hematological toxicity (11%), and DLI-related mortality (9%). Forty-six patients (18%) received a second HCT after a median of 232 days (32–1,390) from the first DLI. With a median follow-up of 461 days (2–3,255) after the first DLI, 1-, 3-, and 5- year OS of the whole group from start of DLI treatment was 55, 39, and 33%, respectively. In multivariate analysis, older recipient age, and transplants from haploidentical donors significantly reduced OS, whereas DLI for mixed chimerism or as pre-emptive/prophylactic treatment compared to DLI for AL relapse and a schedule including more than one DLI significantly prolonged OS. This GITMO survey confirms that DLI administration in absence of overt hematological relapse and multiple infusions are associated with a favorable outcome in AL patients.

Acute Myelogenous Leukemia

Use of DLI for patients with relapsed AML after allogeneic HCT has resulted in overall remission rates ranging from 15% to 42%, with an OS of approximately 15% to 20%. (For comparison, a second HCT in this group of patients results in 10% to 35% long-term survival with a treatment-related mortality of approximately 50%.) Patients with lower initial disease burden, reduction in the tumor burden with chemotherapy before DLI, and favorable cytogenetics appear to have more benefit with DLI.

A large retrospective analysis from the European Blood and Marrow Transplant Group compared OS in 399 patients with AML with post-transplant relapse who either were treated with DLI (n=171) or were not (n=228). (52) Patients who received DLI had an improved 2-year OS compared with those who did not, (21%±3% versus 9%±2%, respectively [p<0.001]).

A 2015 large retrospective series from the Center for International Blood and Marrow Transplant Research (CIBMTR) reported outcomes for 1788 AML patients who experienced a first or second relapsed after allogeneic HCT, among whom 1231 (69%) received subsequent intensive therapy that included DLI. (53) Among the 1231 patients who received treatment, 660 (54%) received chemotherapy alone; 202 (16%) received DLI with or without chemotherapy; and 369 (30%) received a second allogeneic HCT with or without additional chemotherapy or DLI. Among all patients who received DLI, 87 (33%) survived more than 1 year after relapse; median survival was 7 months (range, 1-177 months). Cell-based therapy (DLI or second HCT) resulted in significantly better post-relapse OS than chemotherapy alone. These results are consistent with other reports of DLI in patients who had AML relapse after allogeneic HCT.

The literature for MDS and other MPN diseases treated with DLI either after relapse or for mixed chimerism consists of small sample sizes, inconsistent pre-DLI therapy, and varied DLI cell doses, making it difficult to draw definite conclusions on outcomes. (47) However, it appears some patients attain durable remissions with DLI after post-transplant relapse.

Warlick et al. reported CR after DLI in 49% of 35 patients with relapsed nonchronic myelogenous leukemia, including AML and MDS, after allogeneic HCT. (54) OS at 1 year was 30% and 19% at 2 years. The authors reported a lower-dose regimen of DLI was more tolerable and reduced GVHD occurrence to 25% compared with 66% with higher-dose DLI.

An analysis from the German Cooperative Transplant Study Group reported outcomes among a cohort of patients (N=154) who relapsed after undergoing allogeneic HCT to treat AML (n=124), MDS (n=28), or myeloproliferative syndrome (n=2). (55) All patients received a median of 4 courses of azacitidine, and DLI was administered to 105 (68%). OS among all patients was 29% at 2-year follow-up, which compares favorably with other reports. The overall incidence of acute GVHD based on the total cohort (N=154) was 23%, and 31% in those given DLI (n=105).

Acute Lymphoblastic Leukemia (ALL)
The graft-versus-tumor effect is thought to be less robust in patients with ALL than in the myeloid leukemias. Small studies have reported response rates to DLI ranging from 0% to 20% and OS rates of less than 15%. (46) By comparison, a second allogeneic HCT provides a 5-year OS of approximately 15% to 20%, with a treatment-related mortality rate of approximately 50%.

The clinically evident graft-versus-leukemia effect of DLI requires weeks to months to become apparent, and, as ALL is a rapidly proliferating disease, DLI only is unable to control the disease without a significant reduction in leukemia burden before DLI. Management of patients with relapsed ALL leading to the best OS is with a combination of salvage chemotherapy and DLI. Although it is not clear whether DLI adds benefit to salvage chemotherapy, there are reports of long-term survivors with relapsed ALL who received both chemotherapy and DLI. (47)

Lymphomas (Hodgkin and Non-Hodgkin)
Studies in which patients received DLI for lymphomas consist of small numbers of patients and various histologies (both Hodgkin lymphoma [HL] and high- and low-grade non-Hodgkin lymphoma [NHL]). In general, the highest response rates have been seen in the indolent lymphomas. For NHL, there are too few patients reported with any single histologic subtype of lymphoma to give adequate information of the benefit of DLI for a specific lymphoma subtype. (47)

The largest series reported for NHL (n=21) using DLI showed response rates in 3 of 9 patients with high-grade NHL, 1 of 2 patients with mantle cell lymphoma, and 6 of 10 patients with low-grade disease. (56)

A series of 14 patients with multiply relapsed HL who received RIC allogeneic HCT and DLI showed a CR of 57% and survival at 2 years of 35%. (57)

Multiple Myeloma (MM)
Observational data suggest a graft-versus-tumor effect in MM, as the development of GVHD has correlated with response in several analyses. (47)

Allogeneic HCT is currently considered experimental, investigational and/or unproven for this indication. Most patients with MM who undergo HCT receive an autologous HCT. In addition, the overall role of HCT for MM is currently changing with the advent of new, highly active drugs like lenalidomide and bortezomib.

Five studies (sample size range, 5-63 patients) have reported the role of DLI in relapsed MM, (58-62) with the highest response to DLI being reported as 62%, with approximately half of the responders attaining a CR. (47) One confounding factor for high response rates for multiple myeloma treated with DLI is that corticosteroids used for treating GVHD have a known antimyeloma effect, which could potentially enhance response rates in these patients. (46)

Subsection Summary: DLI
There are a few nonrandomized comparative studies and numerous case series of DLI treatment for various hematologic malignancies and other myeloproliferative disorders. The nonrandomized studies, in patients with acute leukemia and MDS, have reported higher response rates for patients treated with DLI than with alternatives. The case series report higher response rates than expected for relapsed disease compared with historical controls. Although there are no high-quality RCTs for DLI treatment, this evidence permits the conclusion that response rates improve with DLI treatment for patients with previous HCT treatment and relapsed disease.

Modified DLI
In an effort to control GVHD, a group in Italy explored using genetically modified lymphocytes engineered to express the suicide gene thymidine kinase of herpes simplex virus. (63) These lymphocytes were infused into 23 patients with various hematologic malignancies who relapsed after an allogeneic HCT. Six patients died of progressive disease within 4 weeks of infusion. Eleven patients experienced disease response (CR in 6 and partial remission in 5). Three patients remained alive in CR at a median of 471 days. Twelve patients were evaluable for GVHD, 3 of whom developed acute or chronic GVHD, which was successfully treated with ganciclovir.

In a phase 2 trial, donor lymphocytes were treated with rapamycin ex vivo to produce rapamycin-resistant DLIs. (64) Forty patients undergoing low-intensity HCT for hematologic malignancy were treated preemptively with chemotherapy and DLI. There were no infusional toxicities or serious events attributable to DLI. Classical acute GVHD occurred in 4 of 40 patients. By the end of the study (follow-up range, 42-84 months), 18 of 40 patients remained in sustained remission.

A phase 1 study evaluated patient response to DLI expressing the herpes simplex virus thymidine kinase suicide gene. (65) Three patients were enrolled in the trial and received a single DLI. No local or systemic toxicity related to the gene-transfer procedure was observed. Two patients achieved stable disease. No patient had severe GVHD requiring systemic steroid and/or ganciclovir administration. Tyrosine kinase cells were detected in the peripheral blood of all 3 patients by polymerase chain reaction but did not persist more than 28 days.

Subsection Summary: Modified DLI

These early-phase studies are insufficient to determine the efficacy of modified DLI in the treatment of hematologic malignancies. Randomized studies comparing modified DLI to standard treatment would be necessary to determine efficacy.

Hematopoietic Progenitor Cell (HPC) Stem Cell Boost

As with DLI, hematopoietic progenitor-cell (HPC) boost has a positive response rate for relapse following allogeneic HCT. (66) The boost of stem cells, a second dose, may be helpful to reduce the graft failure process, avoiding the risk of serious bleeding and/or infection. Slatter et al. (67) assessed the outcome of 20 boost infusions in 19 of 139 patients who received hematopoietic stem cell transplants for primary immunodeficiencies. The authors demonstrated that patients with primary immunodeficiencies may benefit from a boost infusion, resulting in an increase in donor chimerism, clearance of persistent viral infection and improvement in T- and B-cell function.

Larocca et al. compared patients with poor graft function (PGF) and full donor chimerism following allogeneic HCT who did or did not receive a boost of donor stem cells. (68) They studied 54 patients with PGF: 20 patients received no further boost infusions (group A), 14 received a boost of unmanipulated stem cells from the original donor, without further chemotherapy conditioning (group B), and 20 received donor cells after CD34 selection without conditioning (group C). Trilineage recovery was seen in 40%, 36%, and 75% of the patients, respectively. The conclusion was patients with PGF, a boost of CD34-selected stem cells is associated with a high chance of trilineage recovery and a low risk of acute GVHD.

In 2009, the National Institutes of Health (NIH), released the Mattsson et al. discussion article on graft failure after allogeneic HCT. (69) They reported, “In patients with continued poor graft function in the absence of graft rejection, a boost of donor stem cells without additional preparative chemotherapy may improve graft function. Nine of 15 (60%) evaluable patients became transfusion-independent within one month after the boost marrow was given. Because boost marrow may induce GVHD, T-cell depletion of stem cells can prevent GVHD and improve survival in some patients.” Their review included the Larocca and colleague study discussed in the paragraph above.

Mainardi et al. (2018) reported on 50 pediatric patients with PGF who received 61 boosts with $CD34^+$ selected peripheral blood stem cells (PBSC) after transplantation from matched unrelated (n = 25) or mismatched related (n = 25) donors. (70) Within 8 weeks, a significant

increase in median neutrophil counts (0.6 vs. 1.516×10^9 /l, $P < 0{\cdot}05$) and a decrease in red blood cell and platelet transfusion requirement (median frequencies 1 and 7 vs. 0, $P < 0.0001$ and <0.001), were observed, and 78.8% of patients resolved one or two of their cytopenias. 36.5% had a complete hematological response. Median lymphocyte counts for $CD3^+$, $CD3^+$ $CD4^+$, $CD19^+$ and $CD56^+$ increased 8.3-, 14.2-, 22.- and 1.6-fold. The rate of de novo acute GVHD grade I-III was only 6% and resolved completely. No GVHD grade IV or chronic GVHD occurred. Patients who responded to stem cell boost displayed a trend toward better OS ($P = 0{\cdot}07$). Data suggest improved graft function with HPC boost in this cohort of patients.

Ghobadi et al. (2017) reported on outcomes of a study utilizing either fresh or cryopreserved peripheral blood stem cell products to create CD34+-selected boost infusions to treat patients (n=26) with poor graft function more than 60 days following allogeneic HCT. (71) Seventeen donor-recipient pairs were enrolled onto the prospective study; an additional nine patients treated off protocol were reviewed retrospectively. Three different donor products were used for CD34+ selection: fresh mobilized product using G-CSF only, fresh mobilized products using G-CSF and plerixafor, and cryopreserved cells mobilized with G-CSF. The primary objective was hematologic response rate and secondary objectives included CD34+ yields, incidence and severity of acute and chronic GVHD, OS, and relapse-free survival (RFS). The complete response rate was 62% and overall response (i.e., hematologic recovery rate) was 81%. Treatment was well tolerated; there was no treatment-related mortality and no grade III or IV acute GVHD. Data suggest improved graft function using fresh or cryopreserved peripheral stem cells.

Practice Guidelines and Policy Statements

National Comprehensive Cancer Network (NCCN)

The NCCN has the following guidelines and recommendations when utilizing a DLI option when treating hematological malignancies:

- ALL (v.4.2023) - DLI can be considered an option for patients in relapse after allogeneic HCT. (72)
- CML (v.2.2024) – DLI is effective in inducing durable molecular remissions in the majority of patients with relapsed CML following allogeneic HCT, although it is more effective in patients with chronic phase relapse than advanced phase relapse. (73)
- MDS (v.1.2024) – DLI can be considered an option for patients who relapse after a prolonged remission following allogeneic HCT. (74)
- MM (v.3.2024) – DLI can be considered an option for patients who relapse after allogeneic HCT. (75)

Summary of Evidence: Donor Lymphocyte Infusion (DLI) and Stem Cell Boost

For individuals who have had an allogeneic hematopoietic cell transplantation (HCT) who receive DLI or stem cell boost, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival and change in disease status. In various hematologic malignancies and for various indications such as planned or preemptive DLI, treatment of relapse, or conversion of mixed to full donor chimerism, patients have shown evidence of responding to DLI. Response rates to DLI for relapsed hematologic malignancies following an allogeneic HCT are best in chronic myelogenous leukemia (CML), followed by the

lymphomas, multiple myeloma (MM), and acute leukemias, respectively. Other than CML, clinical responses are most effective when chemotherapy induction is used to reduce the tumor burden before DLI. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have had an allogeneic HCT who receive a modified (genetic or other ex vivo modification) DLI, the evidence includes case series. Relevant outcomes are overall survival and change in disease status. The case series have demonstrated the feasibility of the technique and no serious adverse effects. Without a comparison to standard treatment, the efficacy of administering modified donor lymphocytes is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Short Tandem Repeat (STR) Markers

Following HCT therapy, it is important to determine whether the new blood forming system is of recipient or donor origin; this phenotypic characterization is called chimerism analysis. The characteristics of the engraftment are analyzed, which is called chimerism analysis. Using STR marker assay to characterize the hematological course and to evaluate the usefulness of the blood forming system (particularly for hematological malignancies, MDS or MPN processes, or certain genetic or metabolic disorders) has been tested initially after the HCT, when the patient is declared as disease-free, and at the point of the confirmed stable engraftment of only the donor pattern of the blood forming system. In the case of treatment of miscellaneous solid tumors of adults, which is not considered a hematologic disorder, the data is insufficient to determine the outcomes without further randomized trials of using STR markers prior to or post HCT therapy. (66, 69, 76-80)

Summary of Evidence: Short Tandem Repeat (STR) Markers

For individuals who have an appropriate indication for allogeneic hematopoietic cell transplantation (HCT) who receive donor stem cells, engraftment and chimerism can be challenging. The evidence on the performance of STR markers to assess the usefulness of the blood forming system includes several clinical trials. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a solid organ transplant, confirmation of stable engraftment is assessed by other methods. As solid organ transplants are not a hematological malignancy, STR marker utilization is unnecessary. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
05/15/2024	Document updated with literature review. Coverage unchanged. No new references added.
12/01/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. Added/updated the following references: 1, 3, 14, 17-19, 28, 30, 51, and 69-74; others removed.
06/15/2021	Reviewed. No changes.
04/15/2020	Document updated with literature review. Coverage unchanged. The following references were added/updated: 29, 33-34, 36, and 74-77. Title changed from: Hematopoietic Stem-Cell (HSC) Transplantation (HSCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information).
04/15/2018	Reviewed. No changes.
06/15/2017	Document updated with literature review. Coverage unchanged. The following NOTE was added, Refer to SUR703.001, Organ and Tissue Transplantation for general donor and recipient information.
05/15/2016	Reviewed. No changes.
07/15/2015	Document updated with literature review. Donor lymphocyte infusion and hematopoietic stem-cell boost coverage statements removed from each individual hematopoietic stem-cell transplantation medical policy back to this general donor and recipient informational medical policy; coverage for each procedure remains unchanged. Title changed from Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information).

06/01/2014	Document updated with literature review. The following was added: 1) Genetic modification of donor leukocytes for infusion at any point following any SCS treatment is considered experimental, investigational and/or unproven; 2) Short tandem repeat (STR) markers may be considered medically necessary when used in pre- or post-SCS testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment; and, 3) All other uses of STR markers, including use for a condition that was originally considered experimental, investigational and/or unproven, are considered experimental, investigational and/or unproven.
04/01/2010	Revised/updated entire document. Policy contains criteria for umbilical cord blood donation and storage, prophylactic stem-cell storage, and purging of stem-cells, along with general information regarding stem-cell harvesting, typing, and usage. Medical policy combined with SUR703.022, SUR703.023, and SUR703.024. This policy is no longer scheduled for routine literature review and update.
04/07/2005	CPT/HCPCS code(s) updated (SUR713.022)
11/15/2004	Revised/updated entire document (SUR703.022)
04/01/2003	CPT/HCPCS code(s) updated (SUR713.022)
06/01/2001	CPT/HCPCS code(s) updated (SUR713.022)
05/01/2000	Revised/updated entire document (SUR703.022)
01/01/2000	Revised/updated entire document (SUR703.022)
06/01/1999	Revised/updated entire document (SUR703.022)
05/01/1999	Revised/updated entire document (SUR703.022)
12/01/1998	Revised/updated entire document (SUR703.022)
09/01/1996	New medical document (SUR703.022)
09/01/1996	Revised/updated entire document (SUR703.022)
05/01/1996	Medical policy number changed (SUR713.002)
10/01/1994	Revised/updated entire document (SUR703.022)
10/01/1993	Revised/updated entire document (SUR703.022)
07/01/1993	Revised/updated entire document (SUR703.022)
04/01/1993	Revised/updated entire document (SUR703.022)
01/01/1993	Revised/updated entire document (SUR703.022)
07/01/1992	Revised/updated entire document (SUR703.022)
01/01/1992	Revised/updated entire document (SUR703.022)
09/01/1991	Revised/updated entire document (SUR703.022)
05/01/1990	New medical document (SUR703.002)