

**7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells**

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<b>Section:</b>	11.0 Transplant	<b>Page:</b>	Page 1 of 16

**Policy Statement**

Transplantation of cord blood stem cells from related or unrelated donors may be considered **medically necessary** in patients with an appropriate indication for allogeneic stem cell transplant.

Transplantation of cord blood stem cells from related or unrelated donors is considered **investigational** in all other situations.

Collection and storage of cord blood from a neonate may be considered **medically necessary** when an allogeneic transplant is imminent in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant.

Prophylactic collection and storage of cord blood from a neonate is considered **not medically necessary** when proposed for some unspecified future use as an autologous stem cell transplant in the original donor, or for some unspecified future use as an allogeneic stem cell transplant in a related or unrelated donor.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

**Policy Guidelines**

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

Please refer to the Blue Shield of California Medical Policy site to search for specific conditions and diseases that have associated medical policies with patient selection criteria regarding situations for which allogeneic stem cell transplantation may be considered medically necessary.

**Description**

This evidence review addresses the collection, storage, and transplantation of placental and umbilical cord blood ("cord blood") as a source of stem cells for allogeneic and autologous stem cell transplantation. Potential indications for the use of cord blood are not addressed herein; these are discussed in the disease-specific evidence reviews.

**Related Policies**

- Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- Hematopoietic Cell Transplantation for Autoimmune Diseases

- Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma
- Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

According to the U.S. Food and Drug Administration (FDA), cord blood stored for potential use by a patient unrelated to the donor meets the definitions of "drug" and "biological products." As such, products must be licensed under a biologics license application or an investigational new drug application before use. Facilities that prepare cord blood units only for autologous and/or first- or second-degree relatives are required to register and list their products, adhere to Good Tissue Practices issued by the FDA, and use applicable processes for donor suitability determination.<sup>1</sup>

## Rationale

### Background

#### Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) 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 [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in Blue Shield of California Medical Policy: Placental and Umbilical Cord Blood as a Source of Stem Cells.

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.

### Conditioning for Hematopoietic Cell Transplantation

#### Conventional Conditioning

The conventional ("classical") practice of allo-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 allo-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 Allogeneic Hematopoietic Cell Transplantation**

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 allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

### **Literature Review**

Evidence reviews 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.<sup>2</sup> 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.<sup>3</sup>

### **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 patients with an appropriate indication for allogeneic stem cell transplant.

The question addressed in this evidence review 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 review.

#### **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.

Patients 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.

### **Review of Evidence**

#### **Related Allogeneic Cord Blood Transplant**

The first cord blood transplant involved a child with Fanconi anemia; results were reported in 1989.<sup>4</sup> 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 incidences of acute and chronic GVHD have been observed when cord blood, compared with bone marrow, was used as the source of donor cells.<sup>5</sup> This led to the idea that cord blood could be banked and used as a source of unrelated donor cells, possibly without full HLA matching.<sup>6</sup>

#### **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<sup>7</sup> and 78% in children with nonmalignant conditions.<sup>8</sup> 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 seropositivity in the recipient, non-European ancestry, and higher HLA mismatching. This slower engraftment led to longer hospitalizations and greater utilization of medical resources.<sup>9</sup> 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 with unrelated donor bone marrow transplantation in patients who had acute leukemia.<sup>10</sup> Reviewers identified 7 studies (N=3389 patients). Pooled event 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 transplant 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 OS, 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 children with a variety of nonmalignant conditions.<sup>11,12,13</sup> For example, a study by Liu et al (2014) compared outcomes after unrelated donor cord blood transplantation with matched-sibling donor peripheral blood transplantation.<sup>13</sup> The study included patients ages 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, 100% in the peripheral blood stem cell group). Rates for most outcomes, including grades III and 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 in 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.<sup>14</sup> 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 umbilical cord blood and haploidentical hematopoietic cell transplantation (HCT) in 129 children younger than 14 years old.<sup>15</sup> The 2-year probability of OS was 82% (95% CI, 72.2% to 91.8%) in the haploidentical HCT group and 69.9% (95% CI, 58.0% to 81.2%) in the cord blood group. The difference in OS rates between groups was not statistically significant (p=0.07). The 2-year incidence of relapse was also similar in both groups: 16% (95% CI, 6.1% to 26.1%) in the haploidentical 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.<sup>16</sup> 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% to 68%), 62% (95% CI: 44% to 75%), and 65% (95% CI: 48% to 78%), respectively. The cumulative incidence of relapse was 12% at 100 days and 19.5% at 1 year.<sup>16</sup>

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.<sup>17</sup> 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.<sup>18</sup> 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, non-relapse 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.<sup>19</sup> 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 umbilical cord blood 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.<sup>20</sup> 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 ( Tables 1 and 2).<sup>21</sup>

**Table 1. Summary of Key Trial Characteristics**

Author (Year)	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Wagner et al (2014) <sup>21</sup>		1		Patients (age range, 1 to 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.

**Table 2. Summary of Key Trial Results**

Study (Year)	1-Year OS	1-Year DFS	Acute GVHD	Chronic GVHD
Wagner et al (2014) <sup>21</sup>				
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 ( Tables 3 and 4). In a study by Scaradavou et al (2013), there was a significantly higher risk of acute GVHD (grade II to IV) in recipients of double-cord blood units treated during the first several years of observation.<sup>22</sup> In the later period (2004 to 2009), rates of acute GVHD (grade II to 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.<sup>23</sup>

**Table 3. Summary of Key Observational Study Characteristics**

Author (Year)	Study Type	Dates	Participants	Treatment		Follow-Up
				Arm 1	Arm 2	
Scaradavou et al (2013) <sup>22</sup>	Comparative cohort	2002 to 2004 2004 to 2009		Single unit	Double unit	

Author (Year)	Study Type	Dates	Participants	Treatment		Follow-Up
				Arm 1	Arm 2	
Baron et al (2017) <sup>23</sup> .	Registry	2004 to 2014	Adults with first CBT for AML or ALL	Single unit	Double unit	2 y

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

**Table 4. Summary of Key Observational Study Results**

Study (Year)	N	Relapse Mortality	Nonrelapse Mortality	Acute GVHD (95% CI)	
				2002 to 2004	2004 to 2009
Scaradavou et al (2013) <sup>22</sup> .					
Single unit	106				
Double unit	303				
HR (95% CI)				6.14 (2.54 to 14.87)	1.69 (0.68 to 4.18)
p				<0.001	0.30
Baron et al (2017) <sup>23</sup> .					
Single unit	172			28%	
Double unit	362			36%	
HR (95% CI)		0.9 (0.6 to 1.3)	0.8 (0.5 to 1.2)		
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 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 evidence review 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 review.

#### 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.

**Review of Evidence**

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.

Also, although blood banks are collecting and storing neonate cord blood for potential future use, data on the use of cord blood for autologous stem cell transplantation are limited. A 2017 position paper from the American Academy of Pediatrics noted that there is little evidence of the safety or effectiveness of autologous cord blood transplantation for the treatment of malignant neoplasms.<sup>24</sup> Also, a 2009 survey of pediatric hematologists noted few transplants had been performed using cord blood stored in the absence of a known indication.<sup>25</sup>

**Section Summary: Prophylactic Collection and Storage of Cord Blood**

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 with standard care without cord blood collection and storage.

**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 (OS), 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 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. In another RCT, survival rates were similar after single- and double-unit cord blood 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 cord blood, the evidence includes no published studies. Relevant outcomes are OS, disease-specific survival, resource utilization, and treatment-related mortality. No evidence was identified on the safety or effectiveness of autologous cord blood transplantation from prophylactically stored cord blood for the treatment of malignant neoplasms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Supplemental Information****Practice Guidelines and Position Statements**

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.<sup>29</sup> Key findings and recommendations are summarized in Table 5.

**Table 5. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors**

	Content Area	Key Point
1	Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2	Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs
3	Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4	OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5	Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

### 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.<sup>24</sup> 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

In 2015, with an update in 2019, the American College of Obstetricians and Gynecologists published an opinion on umbilical cord blood (UCB) banking.<sup>26</sup> 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 [UCB] 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

In 2008, on behalf of the American Society for Blood and Marrow Transplantation, Ballen et al. published recommendations related to the banking of UCB<sup>27</sup>:

- Public banking of cord blood is “encouraged.”
- Storing 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 [human leukocyte]-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.<sup>28</sup> 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.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

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

**Table 6. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
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	99,999,999	NR

NCT: national clinical trial; NR: not reported.

## References

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## Documentation for Clinical Review

### Please provide the following documentation:

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
  - Chest x-ray (CXR)
  - PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
  - EKG
  - Echocardiogram
  - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
  - Bone marrow biopsy
  - Lymph node biopsy (as appropriate)
- Laboratory reports

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	None	
HCPCS	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 posttransplant care in the global definition

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
05/29/2015	Coding update
12/04/2015	Policy title change from Placental/Umbilical Cord Blood as a Source of Stem Cells Policy revision without position change
04/01/2016	Policy revision without position change
03/01/2017	Policy revision without position change
03/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
11/01/2019	Policy revision without position change
04/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2021	Annual review. No change to policy statement. Literature review updated.
04/01/2022	Annual review. No change to policy statement.

### Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p><b>Placental and Umbilical Cord Blood as a Source of Stem Cells 7.01.50</b></p> <p><b>Policy Statement:</b>                      Transplantation of cord blood stem cells from related or unrelated donors may be considered <b>medically necessary</b> in patients with an appropriate indication for allogeneic stem cell transplant.</p> <p>Transplantation of cord blood stem cells from related or unrelated donors is considered <b>investigational</b> in all other situations.</p> <p>Collection and storage of cord blood from a neonate may be considered <b>medically necessary</b> when an allogeneic transplant is imminent in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant.</p> <p>Prophylactic collection and storage of cord blood from a neonate is considered <b>not medically necessary</b> when proposed for some unspecified future use as an autologous stem cell transplant in the original donor, or for some unspecified future use as an allogeneic stem cell transplant in a related or unrelated donor.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered <b>investigational</b>.</p>	<p><b>Placental and Umbilical Cord Blood as a Source of Stem Cells 7.01.50</b></p> <p><b>Policy Statement:</b>                      Transplantation of cord blood stem cells from related or unrelated donors may be considered <b>medically necessary</b> in patients with an appropriate indication for allogeneic stem cell transplant.</p> <p>Transplantation of cord blood stem cells from related or unrelated donors is considered <b>investigational</b> in all other situations.</p> <p>Collection and storage of cord blood from a neonate may be considered <b>medically necessary</b> when an allogeneic transplant is imminent in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant.</p> <p>Prophylactic collection and storage of cord blood from a neonate is considered <b>not medically necessary</b> when proposed for some unspecified future use as an autologous stem cell transplant in the original donor, or for some unspecified future use as an allogeneic stem cell transplant in a related or unrelated donor.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered <b>investigational</b>.</p>