APPENDIX to Placental/Umbilical Cord Blood as a Source of Stem Cells Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Transplant Case Management Department.

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 also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

A variety of malignant diseases and non-malignant bone marrow disorders are treated with myeloablative therapy followed by infusion of allogeneic stem and progenitor cells collected from immunologically compatible donors, either from family members or an unrelated donor identified through a bone marrow donor bank. In some cases, a suitable donor is not found.

Alternatively, cord blood is readily available and thought to be antigenically “naive,” thus hopefully 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 antigens (HLA) -A and -B and at high resolution only for HLA-DR; HLA matching at four of six loci is considered acceptable. Under this matching protocol, an acceptable donor can be identified for almost any patient (Godley & van Besien, 2010).

Cord blood banks salvage the hematopoietic progenitor stem cells from the umbilical cord and placental blood and cryogenically freeze them immediately after the birthing process. Several public and private cord blood banks have now been developed in Europe and the United States (U.S.). According to the National Marrow Donor Program (NMDP), cord blood stem cell transplant accounted for 20% of U.S. transplants in 2008, which included both child and adult recipients.

The U.S. Food and Drug Administration (FDA) requires licensing of establishments and their products for unrelated-donor allogeneic transplant of minimally manipulated placental and umbilical cord blood stem cells. Facilities that prepare cord blood units only for autologous or related-donor transplants 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 (FDA, 2009).

For-profit cord blood banks offer the opportunity of collecting and storing a neonate's cord blood for some unspecified future use in the unlikely event that the child develops a condition that would require autologous transplantation. In addition, some cord blood is collected and stored from a neonate for use by a sibling in whom an allogeneic transplant is anticipated due to a history of leukemia or other condition requiring allogeneic transplant.

In 1996, outcome data from the first 25 unrelated cord blood transplants completed at Duke University were reported (Kurtzberg et al., 1996). This study concluded cord blood contained sufficient numbers of stem cells and progenitor cells to reconstitute the marrow of children who underwent myeloablative treatments, without full HLA matching between donor and recipient. Patients who underwent unrelated cord blood transplant experienced a lower incidence and severity of both acute and chronic GVHD, as compared to patients receiving unrelated matched bone marrow. Cell dose was strongly correlated with clinical outcome, including, but not limited to, time to and probability of engraftment as well as overall survival (Kurtzberg et al., 1996; Mayani & Lansdorp, 1998; Rubinstein et al., 1998; Gluckman et al., 1997; Rocha et al., 2001). Since this time, research has been ongoing to study the effectiveness of placental/umbilical cord blood for the treatment of various conditions.

The Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessments in 1996 and 2001 focused on the use of placental/umbilical cord blood in children and adults, respectively. At its inception, placenta/umbilical cord blood was used primarily in children due to concerns that the volume of harvested cells would not support hematopoiesis in larger individuals. The 2001 TEC Assessment focused on the use of placental and umbilical cord blood in adults reporting the following observations and conclusions:

- The available data show that hematopoietic recovery, as measured by neutrophil and platelet engraftment, is somewhat slower and less frequent among adults than among younger patients when placental or cord stem cells are used. Nevertheless, neutrophil counts are restored in the majority (74% to 91%) of adult patients.
- Acute and chronic GVHD and early mortality also are somewhat more frequent among adults than among younger patients given placental or cord stem cells. However, for adult patients who require urgent transplant and are unable to wait for a protracted donor search, the available data that show survival one year after placental or cord stem-cell transplant is not worse than survival one year after an allogeneic stem-cell transplant from an unrelated donor.

The first prospective trial of unrelated cord blood transplant was the Cord Blood Transplantation study (COBLT) from 1997 to 2004. The Cord Blood Transplantation study was designed to examine the safety of unrelated cord blood transplantation in infants, children, and adults. In children with malignant and non-malignant conditions, two-year event-free survival was 55% in

children with high-risk malignancies (Kurtzberg et al., 2008) and 78% in children with non-malignant conditions (Martin et al., 2006). 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 leads to longer hospitalizations and greater utilization of medical resources (Kurtzberg, 2009). In a retrospective multicenter study of 541 children with acute leukemia, rates of neutrophil recovery at day 60 were statistically different: 96% versus 80% for those receiving unrelated bone marrow and unrelated cord blood, respectively (Rocha et al., 2001). In the COBLT study, outcomes in adults were inferior to the outcomes achieved in children. This study also established three new cord blood banks and standard operating procedures addressing donor recruiting and screening, cord blood collection, processing, testing, cryopreservation, storage, and thawing for transplantation (Fraser et al., 1998; Kurtzberg et al., 2005).

Experience at the University of Minnesota has shown that using two units of cord blood for a single transplant in adults improved rates of engraftment and overall survival (Barker et al., 2005). Pilot studies show engraftment being achieved by at least 90% with overall survival at one year ranging from 60% to 80%, depending on the initial disease, comorbidities, and disease status at the time of transplant (Kurtzberg, 2009). In general, when two units are used in a single transplant, one unit engrafts and the other is rejected. The exact role of the non-engrafting unit is unclear. Standard practice continues to be to transplant one unit; however, The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) is currently sponsoring a randomized Phase III clinical trial to determine if outcomes are truly better with two versus one unit.

In addition to trial data, there have been numerous retrospective and registry studies. These studies have supported the conclusions in the early studies that unrelated cord blood transplantation is effective in both children and adults with hematologic malignancies and children with a variety of non-malignant conditions. The majority of cord blood transplants have been mismatched at one or two HLA loci. A 2007 retrospective comparative analysis from the Center for International Blood and Marrow Transplant Research compared outcomes after unrelated cord blood versus unrelated bone marrow transplant. This study showed similar five-year leukemia-free survival for those receiving allele-matched marrow and those who received unrelated cord blood with a one or two antigen mismatch. A minimum cell dose of 2.5 to 3.0 X 10^7 nucleated cells/kilogram in the cord blood has been associated with superior clinical outcome (Kurtzberg et al., 1996; Rubinstein et al., 1998; Gluckman et al., 1997; Rocha et al., 2001; Kurtzberg et al., 2008; Prasad et al., 2008).

Data regarding the use of cord blood for autologous stem cell transplantation are quite limited. However, blood banks are available for collecting and storing a neonate's cord blood for a potential future use. A position paper from the American Academy of Pediatrics (AAP) noted there is no evidence of the safety or effectiveness of autologous cord blood transplantation for treatment of malignant neoplasms (AAP et al., 2007). This report comments on evidence demonstrating the presence of deoxyribonucleic acid (DNA) mutations in cord blood from children who subsequently develop leukemia. In addition, a survey of pediatric hematologists noted few transplants have been performed using cord blood stored in the absences of a known indication (Thornley et al., 2009).

On behalf of the American Society for Blood and Marrow Transplantation, Ballen and colleagues (2008) published recommendations related to the banking of umbilical cord blood:

- Public banking of cord blood is encouraged when possible
- 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

In summary**,** cord blood transplantation offers clear advantages over other sources of allogeneic stem cells. The most significant of these is the ability to perform a successful transplant from an unrelated donor with one or two HLA mismatches. Cord blood is also more readily available, generally within one to two weeks. Collection of the cells is painless, which facilitates recruitment providing for a more ethnically diverse pool. Current limitations include small inventories, units with low cell doses, and too few donors to provide five of six and six of six matches for all patients in need. Longer hospital stays and higher utilization of medical resources are a consequence of slower engraftment when cord blood is used. Even with these limitations, cord blood is an important source of stem cells, increasing the access to allogeneic stem-cell transplantation for many patients. Use in this situation may be considered medically necessary. However, routinely collecting and storing cord blood for a potential future use is considered not medically necessary.

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)) prohibit 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.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

Type	Number	Description
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
	38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogenic
HCPC	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
ICD9 Procedure	41.04	Autologous hematopoietic stem cell transplant without purging
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

Allogeneic - Stem cells are harvested from a tissue compatible (histocompatible) donor.

Autologous - Stem cells are harvested from the patient's own placenta/umbilical cord blood.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

N/A

Key / Related Searchable Words

N/A

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Policy History

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

Effective Date	Action	Reason
1/7/2011	BCBSA Medical Policy adoption	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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