Placental and Umbilical Cord Blood as a Source of Stem Cells

Policy Number: 7.01.50  Last Review: 12/2016
Origination: 12/2001  Next Review: 12/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for placental and umbilical cord blood as a source of stem cells when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
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.

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.

When Policy Topic is not covered
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.

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

Considerations
Through the National Marrow Donor Program’s Related Donor Cord Blood Program, eligible families within the U.S. can collect and store their neonate’s cord blood unit free of charge. When the stored unit is transplanted, a fee is charged. A family is considered eligible if:

- the sibling of the neonate has been diagnosed with a disease treatable by a related cord blood transplant;
- the neonate does not have the same disease as the affected biological sibling (determined after birth);
- the affected sibling and the neonate have the same biological parents;
or if:
- an affected biological parent is enrolled in a clinical or research trial that would accept a haploidentical, related, allogeneic cord blood unit as a treatment option.

Charges for the acquisition of cord blood through a cord blood bank will be submitted as part of the hospital bill.

Reimbursement for stem cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

**Transplant Benefit**

The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:
- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (Note: The member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, Blue Cross and Blue Shield of Kansas City (Blue KC) charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:
- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant
procedure and to maintain compliance with long-term medical management and immunosuppression.

- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by Blue Cross and Blue Shield of Kansas City (Blue KC). Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Clinical trials of autologous or allogeneic stem cell transplantation for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: there are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
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</table>
| Individuals:  
• With an appropriate indication for allogeneic stem cell transplant | Interventions of interest are:  
• Cord blood as a source of stem cells | Comparators of interest are:  
• Stem cells from a source other than cord blood | Relevant outcomes include:  
• Overall survival  
• Disease-specific survival  
• Hospitalizations  
• Resource utilization  
• Treatment-related mortality  
• Treatment-related morbidity |
| Individuals:  
• With an unspecified potential future need for stem cell transplant | Interventions of interest are:  
• Prophylactic collection and storage of cord blood from a neonate | Comparators of interest are:  
• Usual care | Relevant outcomes include:  
• Resource utilization |

This policy addresses the collection, storage, and transplantation of placental/umbilical cord blood ("cord blood") as a source of stem cells for allogeneic and autologous stem-cell transplantation. Potential indications for use of cord blood are included in the disease-specific reference policies.
The evidence for cord blood as a source of stem cells in individuals undergoing allogeneic stem cell transplant includes a number of observational studies, a meta-analysis of observational studies, and a randomized controlled trial (RCT) comparing outcomes after single or double cord blood units. Relevant outcomes are overall survival, disease-specific survival, hospitalizations, resource utilization, and treatment-related mortality and morbidity. The meta-analysis of observational studies found similar survival outcomes and lower graft versus host disease after cord blood transplantation than bone marrow transplantation. In the RCT, survival rates were similar after single-unit and double-unit cord blood transplantation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for prophylactic collection and storage of cord blood from a neonate for individuals with an unspecified potential future need for stem cell transplant includes no published studies. Relevant outcomes are resource utilization. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

A variety of malignant diseases and nonmalignant 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.

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 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 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 now been developed in Europe and in the United States. In addition to obtaining cord blood for specific related or unrelated patients, some cord blood banks are offering the opportunity to collect and store 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.

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 such issues as monitoring cell loss, change in
potency, and prevention of product mix-up. (1) Two major organizations are working toward these accreditation standards; NetCord/FACT and the American Association of Blood Banks (AABB). NetCord, Foundation for the Accreditation of Cellular Therapy (FACT) has developed and implemented a program of voluntary inspection and accreditation for cord blood banking. In September 2012, NetCord and FACT released the fifth edition of their international standards for cord blood banks. (3) The voluntary program includes standards for collection, testing, processing, storage, and release of cord blood products.

**Regulatory Issues**

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. (3)

Other cord blood banks are offering 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.

As with any biologic product, there are issues unique to cord blood as an unrelated donor source; some of these are as follows:

- Cell dose available is much closer to the minimum needed for engraftment
- Interbank variability in the quantification of hematopoietic potential
- Donors who may have hematologic/immunologic disorders may not have manifested their disease at the time of donation or follow-up
- Units may have been banked years earlier at a time when the collection and storage process may not have reflected current accreditation standards, and,
- The initial product characterization at the end of processing may not reflect the product at the time of release due to freeze, storage, or transport insults. (3)

For the reasons cited above, instituting international standards and accreditation for cord blood banks is critical. This will assist transplant programs in knowing whether individual banks have important quality control measures in place to address such issues as monitoring cell loss, change in potency, and prevention of product mix-up. (3) Two major organizations are working toward these accreditation standards; NetCord/FACT and the American Association of Blood Banks (AABB). NetCord, Foundation for the Accreditation of Cellular Therapy (FACT) has developed and implemented a program of voluntary inspection and accreditation for cord blood banking. The program includes standards for collection, testing, processing, storage, and release of cord blood products. Forty-two banks have applied for accreditation, 21 are fully accredited while the rest are in process. AABB also runs an accreditation process, in which an AABB
representative inspects the program. Twenty-seven banks in the U.S. have been accredited, along with 33 international sites. (3)

The U.S. Food and Drug Administration intends to regulate cord blood banking by requiring Biologic License Applications and/or Investigational New Drug applications by October 2011 for any bank that will supply units to patients in the United States. With the international exchange of cord blood units being integral to the availability of a matched unit, it is unclear how this change will affect the practice of acquiring cord blood units. (4)

It is also important to note umbilical cord blood (UCB) samples are not routinely typed for private banking. This makes it difficult to search for unrelated human leukocyte antigen (HLA)-matched donors in private banks, or to transfer units into a public bank from a private bank. (5)

**Rationale**

This evidence review was originally based on TEC Assessments in 1996 and 2001, (4,5) which addressed the use of placental/umbilical cord blood in children and adults, respectively. This evidence review has been updated regularly with searches of the MEDLINE database, most recently through December 6, 2015.

**Related Allogeneic Cord Blood Transplant**

The first cord blood transplant was a related cord blood transplant for a child with Fanconi anemia; results were reported in 1989.(6) At least 60 other cord transplants have subsequently been performed in matched siblings. The results of these transplants demonstrated that cord blood contains sufficient numbers of hematopoietic stem and progenitor cells to reconstitute pediatric patients. A lower incidence of acute and chronic graft-versus-host disease (GVHD) was observed when cord blood, as compared with bone marrow, was used as the source of donor cells.(7) 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.(8)

**Unrelated Allogeneic Cord Blood Transplant**

Research has been conducted to study the effectiveness of placental/umbilical cord blood for the treatment of various conditions The first prospective study of unrelated cord blood transplant was the Cord Blood Transplantation study (COBLT), published in 2005. COBLT was designed to examine the safety of unrelated cord blood transplantation in infants, children, and adults. In children with malignant and nonmalignant conditions, 2-year event-free survival was 55% in children with high-risk malignancies(9) and 78% in children with nonmalignant conditions.(10) 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.(11) In the COBLT study, outcomes in adults were inferior to the outcomes achieved in children.
In 2012, Zhang et al published a meta-analysis of studies comparing unrelated donor cord blood transplantation to unrelated donor bone marrow transplantation in patients with acute leukemia. The authors identified 7 studies (total N=3389 patients). Pooled rates of engraftment failure (n=5 studies) were 127 events in 694 (18%) patients in the cord blood transplantation group and 57 events in 951 (6%) patients in bone marrow transplantation patients. 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 transplantation group. Pooled rates of GVHD (n=7 studies) were 397 (34%) of 1179 in the cord blood group and 953 (44%) of 2189 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 (OS), leukemia-free survival, and nonrelapse mortality favored the bone marrow transplantation group.

In addition, 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. For example, a 2014 study by Liu et al compared outcomes after unrelated donor cord blood transplantation and matched-sibling donor peripheral blood transplantation. The study included patients ages 16 years or older who had hematologic malignancies. A total of 70 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 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). Moreover, these studies identified the importance of a minimum cell dose. For example, a 2014 analysis of data from the Korean Cord Blood Registry found that the presence of at least 3.91±105/kg of infused CD34+ cells was significantly associated with OS (p=0.03) in unrelated donor cord blood transplants in children and adolescents. In other studies, a minimum cell dose of 2.5 to 3.0±107 nucleated cells per kilogram in the cord blood has been associated with superior clinical outcome.

More recently, transplantation of 2 umbilical cord blood units (also known as 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 the University of Minnesota showed that using 2 units of cord blood for a single transplant in adults improved rates of engraftment and OS. 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. In 2014, Wagner et al published a randomized controlled trial (RCT) comparing outcomes after double-
unit (n=111) or single unit (n=113) cord blood transplants.(23) The study included patients ages 1 to 21 years who had high-risk acute leukemia, chronic myeloid leukemia, or myelodysplastic syndrome for whom there were 2 cord blood units available with adequate cell doses and HLA matches on at least 4 of 6 loci. The primary outcome, 1-year OS rate, was 65% (95% confidence interval [CI], 56% to 74%) after double-unit transplant and 73% (95% CI, 63% to 80%) after single-unit transplant. The difference between groups was not statistically significant (p=0.17). Similarly, 1-year disease-free survival was 64% (95% CI, 54% to 72%) in the double-unit transplant group and 70% (95% CI, 60% to 77%) in the single-unit transplant group (p=0.11). However, rates of acute grade II and IV GHVD was significantly higher in the double-unit transplant group (23%; 95% CI, 15% to 31%) than the single-unit transplant group (13%; 95% CI, 7% to 20%; p=0.02). The incidence of chronic GVHD after 1 year was similar in the 2 groups (32% [95% CI, 23% to 40%] after double-unit transplant, 30% [95% CI, 22% to 29%] after single-unit transplant; p=0.51).

Results of a 2013 observational study were similar to those found in the Wagner RCT. Scaradavou et al did not find significant differences in survival after single- or double-cord blood transplant.(24) In patients treated during the first several years of observation (2002-2004), there was a significantly higher risk of grade 2-4 acute GVHD in recipients of double-cord blood units (hazard ratio [HR], 6.14; 95% CI, 2.54 to 14.87; p<0.001). In the later period (2004-2009), rates of grade 2-4 acute GVHD did not differ significantly between groups (HR=1.69; 95% CI, 0.68 to 4.18; p=0.30).

Autologous Cord Blood Transplant
Data on use of cord blood for autologous stem cell transplantation are quite limited. However, blood banks are collecting and storing neonate cord blood for potential future use. A 2007 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.(25) In addition, a 2009 survey of pediatric hematologists noted few transplants have been performed using cord blood stored in the absences of a known indication.(26)

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>Trial Name</th>
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<tr>
<td>NCT01728545</td>
<td>The Collection and Storage of Umbilical Cord Blood for Transplantation</td>
<td>250,000</td>
<td>Jun 2099</td>
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<td>NCT00012545</td>
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NCT: national clinical trial.
Summary of Evidence
The evidence for cord blood as a source of stem cells in individuals who are undergoing allogeneic stem cell transplant includes a number of observational studies, a meta-analysis of observational studies, and a randomized controlled trial (RCT) comparing outcomes after single- or double-cord blood units. Relevant outcomes are overall survival, disease-specific survival, hospitalizations, resource utilization, and treatment-related mortality and morbidity. The meta-analysis of observational studies found similar survival outcomes and lower graft-versus-host-disease after cord blood transplantation than bone marrow transplantation. In the RCT, survival rates were similar after single-unit and double-unit cord blood transplantation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for prophylactic collection and storage of cord blood from a neonate for individuals who have an unspecified potential future need for stem cell transplant includes no published studies. Relevant outcomes are resource utilization. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists
In 2015, the American College of Obstetricians and Gynecologists published a committee opinion on umbilical cord blood banking.(27) The statement discussed counseling patients about options for umbilical cord blood banking, as well as benefits and limitations of this practice. Relevant recommendations include the following:

- “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.”
- “The routine storage of umbilical cord blood as ‘biologic insurance’ against future disease is not recommended.”

American Society for Blood and Marrow Transplantation
On behalf of the American Society for Blood and Marrow Transplantation, in 2008, Ballen et al published recommendations related to the banking of umbilical cord blood28:

- 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 in the case of 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 human leukocyte antigens between the parents.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References:
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transplanting Adult Patients with Hematopoietic Stem Cells from Placental and Umbilical Cord Blood. TEC Assessments 2001;Volume 16(Tab 17).

Billing Coding/Physician Documentation Information

**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

Additional Policy Key Words

N/A
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<th>Date</th>
<th>Description</th>
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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.