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 an 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.

Policy Guidelines

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; they are discussed in the disease-specific evidence reviews.

Related Policies

- Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
- 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 Epithelial Ovarian Cancer
- Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- Hematopoietic Cell Transplantation For Waldenström Macroglobulinemia
- Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors
- High-Dose Rate Temporary Prostate Brachytherapy
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, 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 Food and Drug Administration, and use applicable processes for donor suitability determination.3

Rationale

Background

Bone Marrow Disorders

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 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 and permitting the broader use of unrelated cord blood transplants. Unrelated donors are typically typed at low resolution for human leukocyte antigen–A and –B and at high resolution only for human leukocyte antigen–DR; human leukocyte antigen 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 United States 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.1 Two major organizations have created accreditation standards for cord blood banks in the US: the American Association of Blood Banks and the International NetCord Foundation/Foundation for
the Accreditation of Cellular Therapy (NetCord/FACT). Both the AABB and the NetCord/FACT have developed and implemented a program of voluntary inspection and accreditation for cord blood banking. The AABB and the NetCord/FACT publish standards for cord blood banks that define the collection, testing, processing, storage, and release of cord blood products.2

**Literature Review**

This review was informed by a 1996 and a 2001 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment, which addressed the use of placental and umbilical cord blood in children and adults, respectively.4,5

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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**

**Related Allogeneic Cord Blood Transplant**

The first cord blood transplant involved a child with Fanconi anemia; results were reported in 1989.6 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 graft-versus-host disease (GVHD) have been observed when cord blood, 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 matching.8

**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 malignancies9 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 human leukocyte antigen mismatching. This slower engraftment led to longer hospitalizations and greater utilization of medical resources.11 In the Cord Blood Transplantation 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 with unrelated donor bone marrow transplantation in patients who had acute leukemia.12 Reviewers identified 7 studies (total 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 overall survival (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. For example, a 2014 study by Liu et al compared outcomes after unrelated donor cord blood transplantation with matched-sibling donor peripheral blood transplantation. The study included patients ages 16 years or older who had hematologic malignancies. Seventy patients received unrelated cord blood, and 115 patients received human leukocyte antigen–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). In 2016, Mo et al reported on outcomes after umbilical cord blood and haploidentical hematopoietic cell transplantation in 129 children younger than 14 years old. The 2-year probability of OS was 82% (95% confidence interval [CI], 72.2% to 91.8%) in the haploidentical hematopoietic cell transplantation 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 haplo-HCT group and 24.1% (95% CI, 12.5% to 37.5%) in the cord blood group (p=0.17).

Also, 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. 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 1 and 2).

### Table 1. Summary of Key Trial Characteristics

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner et al (2014)</td>
<td>18</td>
<td>1</td>
<td>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</td>
<td>2 units</td>
<td>1 unit</td>
</tr>
</tbody>
</table>

HLA: human leukocyte antigen.

### Table 2. Summary of Key Trial Results (N=224)

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>1-Year OS</th>
<th>1-Year DFS</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner et al (2014)</td>
<td>Single unit (95% CI), %</td>
<td>73 (63 to 80)</td>
<td>70 (60 to 77)</td>
<td>13 (7 to 20)</td>
</tr>
<tr>
<td></td>
<td>Double unit (95% CI), %</td>
<td>65 (56 to 74)</td>
<td>64 (54 to 72)</td>
<td>23 (15 to 31)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.17</td>
<td>0.011</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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 RCT (see Tables 3 and 4). 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. 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. A 2017 analysis by Baron et al 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.

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

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Type</th>
<th>Dates</th>
<th>Participants</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron et al (2017)</td>
<td>Registry</td>
<td>2004-2014</td>
<td>Adults with first CBT</td>
<td>Single unit for AML or ALL</td>
<td>Double unit</td>
<td>2 y</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaradavou et al (2013)</td>
<td></td>
<td></td>
<td></td>
<td>6.14 (2.54 to 14.87)</td>
<td>1.69 (0.68 to 4.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.30</td>
</tr>
<tr>
<td>Baron et al (2017)</td>
<td>172</td>
<td>28%</td>
<td></td>
<td>0.9 (0.6 to 1.3)</td>
<td>0.8 (0.5 to 1.2)</td>
</tr>
<tr>
<td></td>
<td>362</td>
<td>36%</td>
<td></td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; GVHD: graft-versus-host disease; HR: hazard ratio; OS: overall survival.

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

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

### Prophylactic collection and storage of cord blood

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 treatment of malignant neoplasms. Also, a 2009 survey of pediatric hematologists noted few transplants had been performed using cord blood stored in the absence of a known indication.

### 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 a randomized controlled trial comparing outcomes after single- or double-cord blood units. Relevant outcomes are overall survival, disease-specific survival, resource utilization, and treatment-related mortality. 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 randomized controlled trial, survival rates were similar after single- and double-unit cord blood transplantation. The evidence is sufficient to determine that the technology results in a meaningful 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 overall survival, 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 the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

American Academy of Pediatrics
A position statement on cord blood banking for potential future transplantation was published by the American Academy of Pediatrics in 2017. 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.

U.K. Consensus Recommendations on Umbilical Cord Blood Transplantation
In 2015, a consensus conference in the United Kingdom issued the following recommendation on umbilical cord blood transplantation:

“We recommend that UCB [umbilical cord blood]... be considered as an alternative source of HSC [hematopoietic stem cells] for transplantation for those patients without a suitably matched sibling or unrelated donor, defined as ‘standard’ or ‘clinical option’ transplants within the BSBMT [British Society of Blood and Marrow Transplantation] transplant indications tables.”

American College of Obstetricians and Gynecologists
In 2015, the American College of Obstetricians and Gynecologists published an opinion on umbilical cord blood banking. The statement discussed counseling patients on options for umbilical cord blood banking, as well as benefits and limitations of this practice. Relevant recommendations included 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, Ballen et al (2008) published recommendations related to the banking of umbilical cord blood:

1. Public banking of cord blood is “encouraged.”
2. Storing cord blood for autologous (i.e., personal) use “is not recommended.”
3. “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.”

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 unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01728545</td>
<td>The Collection and Storage of Umbilical Cord Blood for Transplantation</td>
<td>250,000</td>
<td>Jun 2099</td>
</tr>
<tr>
<td>NCT00012545</td>
<td>Collection and Storage of Umbilical Cord Stem Cells for Treatment of Sickle Cell Disease</td>
<td>99,999,999</td>
<td>none</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


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**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td></td>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>
### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal at 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.