# Prior Authorization Review Panel MCO
## Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

<table>
<thead>
<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 09/04/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Number: 0190</td>
<td>Effective Date:</td>
</tr>
<tr>
<td></td>
<td>Revision Date:</td>
</tr>
<tr>
<td>Policy Name: Stem Cells for Hematopoietic Cell Transplant</td>
<td>04/04/2017</td>
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</tbody>
</table>

**Type of Submission – Check all that apply:**
- [ ] New Policy
- [x] Revised Policy
- [x] Annual Review – No Revisions*

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0190 Stem Cells for Hematopoietic Cell Transplant**

Clinical content was last revised on 04/04/2017. No additional non-clinical updates were made by Corporate since the last PARP submission, as documented below.

**Revision and Update History since last PARP submission:**
- 08/03/2018 - This CPB has been reviewed and maintained.
- 02/14/2019 – Tentative next scheduled review date by Corporate.

<table>
<thead>
<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>![Signature]</td>
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</tbody>
</table>

[www.aetnabetterhealth.com/pennsylvania](http://www.aetnabetterhealth.com/pennsylvania) annual 09/04/2018
Stem Cells for Hematopoietic Cell Transplant

Policy

Aetna considers compatibility testing of prospective donors who are close family members (first-degree relatives (i.e., parents, siblings and children) or second degree relatives (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling)) and harvesting and short-term storage of peripheral stem cells or bone marrow from the identified donor medically necessary when an allogeneic bone marrow or peripheral stem cell transplant is authorized by Aetna.

Aetna considers umbilical cord blood stem cells an acceptable alternative to conventional bone marrow or peripheral stem cells for allogeneic transplant.

Aetna considers medically necessary the short-term storage of umbilical cord blood for a member with a malignancy undergoing treatment when there is a match. **Note:** The harvesting, freezing and/or storing umbilical cord blood of non-

Please see amendment for Pennsylvania Medicaid at the end of this CPB.
diseased persons for possible future use is not considered treatment of disease or injury. Such use is not related to the person’s current medical care.

Aetna considers co-transplantation of multipotent mesenchymal stromal cells in allogeneic hematopoietic stem cell transplantation experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers the use of enzyme-linked immunospot (ELISPOT) interferon-gamma release assay for prediction of the risk of cytomegalovirus infection in hematopoietic cell transplant recipients experimental and investigational because its effectiveness has not been established.

Notes:

- When a covered family member of a newborn infant has a medically necessary indication for an allogeneic bone marrow transplant and wishes to use umbilical cord blood stem cells as an alternative, Aetna covers the testing of umbilical cord blood for compatibility for transplant under the potential recipient's plan.
- Performance of HLA typing and identification of a suitable donor does not, in and of itself, guarantee coverage of allogeneic bone marrow or peripheral stem cell transplantation. Medical necessity criteria and plan limitations and exclusions may apply.

See also the following CPBs related to bone marrow and peripheral stem cell transplantation:

- CPB 0494 - Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphoma (../400_499/0494.html)
- CPB 0495 - Hematopoietic Cell Transplantation for Hodgkin's Disease (../400_499/0495.html)
- CPB 0496 - Hematopoietic Cell Transplantation for Selected Childhood Solid Tumors (../400_499/0496.html)
- CPB 0497 - Hematopoietic Cell Transplantation for Multiple Myeloma (../400_499/0497.html)
- CPB 0507 - Hematopoietic Cell Transplantation for Breast Cancer (../500_599/0507.html)
- CPB 0606 - Hematopoietic Cell Transplantation for Autoimmune Diseases and Miscellaneous Indications (../600_699/0606.html)
- CPB 0617 - Hematopoietic Cell Transplantation for Testicular Cancer (../600_699/0617.html)
- CPB 0626 - Hematopoietic Cell Transplantation for Thalassemia Major and Sickle Cell Anemia (../600_699/0626.html)
- CPB 0627 - Hematopoietic Cell transplantation for Aplastic Anemia and other Bone Marrow Failure Syndromes (../600_699/0627.html)
- CPB 0634 - Non-myeloablative Bone Marrow/Peripheral Stem Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant) (../600_699/0634.html)
- CPB 0635 - Hematopoietic Cell Transplantation for Ovarian Cancer (../600_699/0635.html)
- CPB 0638 - Donor Lymphocyte Infusion (../600_699/0638.html)
- CPB 0640 - Hematopoietic Cell Transplantation for Selected Leukemias (../600_699/0640.html)
- CPB 0674 - Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia (../600_699/0674.html)
- CPB 0811 - Hematopoietic Cell Transplantation for Solid Tumors in Adults (../800_899/0811.html)
B ac kg round

According to the American Academy of Pediatrics (2007), cord blood transplantation has been shown to be curative in patients with a variety of serious diseases. Physicians should be familiar with the rationale for cord blood banking and with the types of cord blood banking programs available.

Physicians consulted by prospective parents about cord blood banking can provide the following information:

- Cord blood donation should be discouraged when cord blood stored in a bank is to be directed for later personal or family use, because most conditions that might be helped by cord blood stem cells already exist in the infant's cord blood (i.e., pre-malignant changes in stem cells). Physicians should be aware of the unsubstantiated claims of private cord blood banks made to future parents that promise to insure infants or family members against serious illnesses in the future by use of the stem cells contained in cord blood. Although not standard of care, directed cord blood banking should be encouraged when there is knowledge
of a full sibling in the family with a medical condition (malignant or genetic) that could potentially benefit from cord blood transplantation.

- Cord blood donation should be encouraged when the cord blood is stored in a bank for public use. Parents should recognize that genetic (e.g., chromosomal abnormalities) and infectious disease testing is performed on the cord blood and that if abnormalities are identified, they will be notified. Parents should also be informed that the cord blood banked in a public program may not be accessible for future private use.

- Because there are no scientific data at the present time to support autologous cord blood banking and given the difficulty of making an accurate estimate of the need for autologous transplantation and the ready availability of allogeneic transplantation, private storage of cord blood as "biological insurance" should be discouraged. Cord blood banks should comply with national accreditation standards developed by the Foundation for the Accreditation of Cellular Therapy (FACT), the U.S. Food and Drug Administration (FDA), the Federal Trade Commission, and similar state agencies. At a minimum, physicians involved in procurement of cord blood should be aware of cord blood collection, processing, and storage procedures.

Eapen and colleagues (2010) stated that umbilical-cord blood (UCB) is increasingly considered as an alternative to peripheral blood progenitor cells (PBPCs) or bone marrow, especially when an human leukocyte antigen (HLA)-matched adult unrelated donor is not available. These investigators aimed to determine the optimal role of UCB grafts in transplantation for adults with acute leukemia, and to establish whether current graft-selection practices are appropriate. They used Cox regression to retrospectively
compare leukemia-free survival and other outcomes for UCB, PBPC, and bone marrow transplantation in patients aged 16 years or over who underwent a transplant for acute leukemia. Data were available on 1,525 patients transplanted between 2002 and 2006. A total of 165 received UCB, 888 received PBPCs, and 472 received bone marrow. Umbilical-cord blood units were matched at HLA-A and HLA-B at antigen level, and HLA-DRB1 at allele level (n = 10), or mis-matched at 1 antigen (n = 40) or 2 antigens (n = 115). Peripheral blood progenitor cells and bone-marrow grafts from unrelated adult donors were matched for allele-level HLA-A, HLA-B, HLA-C, and HLA-DRB1 (n = 632 and n = 332, respectively), or mis-matched at 1 locus (n = 256 and n = 140, respectively).

Leukemia-free survival in patients after UCB transplantation was comparable with that after 8/8 and 7/8 allele-matched PBPC or bone-marrow transplantation. However, transplant-related mortality was higher after UCB transplantation than after 8/8 allele-matched PBPC recipients (hazard ratio [HR] 1.62, 95 % confidence interval [CI]: 1.18 to 2.23; p = 0.003) or bone-marrow transplantation (HR 1.69, 95 % CI: 1.19 to 2.39; p = 0.003). Grades 2 to 4 acute and chronic graft-versus-host disease (GVHD) were lower in UCB recipients compared with allele-matched PBPC (HR 0.57, 95 % CI: 0.42 to 0.77; p = 0.002 and HR 0.38, 95 % CI: 0.27 to 0.53; p = 0.003, respectively), while the incidence of chronic, but not acute GVHD, was lower after UCB than after 8/8 allele-matched bone-marrow transplantation (HR 0.63, 95 % CI: 0.44 to 0.90; p = 0.01). These data support the use of UCB for adults with acute leukemia when there is no HLA-matched unrelated adult donor available, and when a transplant is needed urgently.

Co-Transplantation of Multipotent Mesenchymal Stromal Cells in Allogeneic Hematopoietic Stem Cell Transplantation:

Zhao et al (2015) noted that refractory acute GVHD (aGVHD) is a major cause of death after allogeneic hematopoietic stem cell transplantation (allo-HSCT). These researchers evaluated
the immunomodulation effects of mesenchymal stromal cells (MSCs) from bone marrow of a third-party donor for refractory aGVHD. A total of 47 patients with refractory aGVHD were enrolled: 28 patients receiving MSC and 19 patients without MSC treatment; MSCs were given at a median dose of $1 \times 10^6$ cells/kg weekly until patients got complete response or received 8 doses of MSCs. After 125 doses of MSCs were administered, with a median of 4 doses (range of 2 to 8) per patient, overall response rate was 75% in the MSC group compared with 42.1% in the non-MSC group ($p = 0.023$). The incidence of cytomegalovirus, Epstein-Barr virus infections, and tumor relapse was not different between the 2 groups during aGVHD treatment and follow-up. The incidence and severity of chronic GVHD (cGVHD) in the MSC group were lower than those in the non-MSC group ($p = 0.045$ and $p = 0.005$). The ratio of CD3(+)CD4(+)CD3(+)CD8(+) T cells, the frequencies of CD4(+)CD25(+)Foxp3(+) regulatory T cells (Tregs), and the levels of signal joint T cell-receptor excision DNA circles (sjTRECs) after MSCs treatment were higher than those pre-treatment; MSC-treated patients exhibited higher Tregs frequencies and sjTRECs levels than those in the non-MSC group at 8 and 12 weeks after treatment. The authors concluded that MSCs derived from bone marrow of a third-party donor were effective to refractory aGVHD; it might reduce the incidence and severity of cGVHD in aGVHD patients by improving thymic function and induction of Tregs but not increase the risks of infections and tumor relapse. These preliminary findings need to be validated by well-designed studies.

Kallekleiv et al (2016) stated that allo-HSCT is a potentially curative treatment option for patients with hematological malignancies. Co-transplantation of multi-potent MSCs during allo-HSCT has been explored to enhance engraftment and decrease the risk of GVHD. These investigators evaluated and summarized the findings of all relevant controlled clinical studies to determine the potential benefits of MSC infusion during allo-HSCT, with regard to the outcomes engraftment,
GVHD, post-transplant relapse and survival. They conducted a systematic search of electronic databases for relevant controlled clinical studies. Studies included patients of all ages with hematological malignancies receiving allo-HSCT with or without infusion of MSCs within a 24-hour time-frame of transplantation. A total of 9 studies met the inclusion criteria, including 3 randomized, 1 non-randomized and 5 historically controlled trials, representing a total of 309 patients. The meta-analyses did not reveal any statistically significant differences in donor engraftment or GVHD. A review of data regarding relapse and overall survival (OS) may result in a positive attitude toward intervention with MSCs, but due to heterogeneous reporting, it is difficult to draw any strict conclusions. None of the studies had overall serious risks of bias, but the quality of the evidence was low. The authors concluded that meta-analysis did not reveal any statistically significant effects of MSC co-transplantation, but the results must be interpreted with caution because of the weak study design and small study populations. They discussed further needs to explore the potential effects of MSCs in a HSCT setting.

Enzyme-Linked Immunospot Interferon-Gamma Release Assay for Prediction of the Risk of Cytomegalovirus Infection in Hematopoietic Cell Transplant Recipients:

Nesher et al (2016) stated that the ability to distinguish allogeneic hematopoietic cell transplant (allo-HCT) recipients at risk for cytomegalovirus (CMV) re-activation from those who are not is central for optimal CMV management strategies. Interferon-gamma (IFN-γ) produced by CMV-challenged T cells may serve as an immune marker differentiating these 2 populations. These researchers prospectively monitored 63 CMV-seropositive allo-HCT recipients with a CMV-specific enzyme-linked immunospot (ELISpot) assay and for CMV infection from the period before transplantation to day 100 after transplantation. Assay results above certain thresholds (50 spots per 250,000 cells for immediate early 1 or 100 spots
per 250,000 cells for phosphoprotein 65) identified patients who were protected against CMV infection as long as they had no GVHD and/or were not receiving systemic corticosteroids. Based on the multi-variable Cox proportional hazards regression model, the only significant factor for preventing CMV reactivation was a CMV-specific ELISPOT response above the determined thresholds (adjusted HR, 0.21; 95% CI: 0.5 to 0.97; p = 0.046). The authors concluded that the use of this assay as an additional tool for managing allo-HCT recipients at risk for CMV reactivation needs further validation in future studies. They stated that application of this new approach may reduce the duration and intensity of CMV monitoring and the duration of prophylaxis or treatment with anti-viral agents in those who have achieved CMV-specific immune reconstitution.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>CPT codes covered if selection criteria are met:</td>
<td></td>
</tr>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
</tr>
<tr>
<td>38206</td>
<td>autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
</tr>
<tr>
<td>38209</td>
<td>thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>specific cell depletion within harvest, T-cell depletion</td>
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<tr>
<td>38211</td>
<td>tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<tr>
<td>59012</td>
<td>Cordocentesis (intrauterine), any method</td>
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<td>86813</td>
<td>HLA typing; A, B, or C, multiple antigens</td>
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<tr>
<td>86817</td>
<td>DR/DQ, multiple antigens</td>
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<td>86821</td>
<td>lymphocyte culture, mixed (MLC)</td>
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<td>86920</td>
<td>Compatibility test each unit; immediate spin technique</td>
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<td>86921</td>
<td>incubation technique</td>
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<td>86922</td>
<td>antiglobulin technique</td>
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<td>86923</td>
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HCPCS codes covered if selection criteria are met:

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<th>Code</th>
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<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<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 rehabilitative services; and the number of days of pre-and post-transplant care in the global definition</td>
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ICD-10 codes covered if selection criteria are met (not all-inclusive):

<table>
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<th>Code</th>
<th>Description</th>
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<td>C00.0 - C75.9</td>
<td>Malignant neoplasm</td>
</tr>
<tr>
<td>Z52.001</td>
<td>Unspecified donor, stem cells [prospective donors who are close family members (first-degree relatives or second degree relatives)]</td>
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<tr>
<td>Z52.3</td>
<td>Bone marrow donor [prospective donors who are close family members (first-degree relatives or second degree relatives)]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


23. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Transplanting adult patients with hematopoietic stem cells from placental and
umbilical cord blood. TEC Assessment Program.
Chicago IL: BCBSA; 2001;16(17).


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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0190 Stem Cells for Hematopoietic Cell Transplant

There are no amendments for Medicaid.