**Policy Statement**

**Embryonal Tumors of the Central Nervous System**

**Autologous Hematopoietic Cell Transplantation**

Autologous hematopoietic cell transplantation for the treatment of embryonal tumors of the central nervous system (CNS) may be considered **medically necessary** when one of the following criteria is met:

- As consolidation therapy for previously untreated embryonal tumors of the central nervous system (CNS) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy (see Policy Guidelines section)
- To treat recurrent embryonal tumors of the CNS

Tandem autologous hematopoietic cell transplantation is considered **investigational** to treat embryonal tumors of the CNS.

**Allogeneic Hematopoietic Cell Transplantation**

Allogeneic hematopoietic cell transplantation is considered **investigational** to treat embryonal tumors of the CNS.

**Ependymoma**

Autologous, tandem autologous, and allogeneic hematopoietic cell transplantation is considered **investigational** to treat ependymoma.

**Policy Guidelines**

In general, use of autologous hematopoietic cell transplantation for previously untreated medulloblastoma has shown no survival benefit for those patients considered to be at average risk (i.e., patient age greater than 3 years, without metastatic disease, and with total or near total surgical resection [less than 1.5 cm² residual tumor]) compared with conventional therapies.

**Description**

High-dose chemotherapy with hematopoietic cell transplantation (HCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in those with high-risk disease. Moreover, the use of HCT has allowed for a reduction in the dose of radiation needed to treat both average- and high-risk disease, all while preserving the quality of life and intellectual functioning— and without compromising survival.

**Related Policies**

- Hematopoietic Cell Transplantation for Solid Tumors of Childhood

**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**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

**Rationale**

**Background**

**Central Nervous System Embryonal Tumors**

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. CNS embryonal tumors are more common in children and are the most common brain tumor in childhood. Medulloblastomas account for 20% of all childhood CNS tumors.

Recurrent childhood CNS embryonal tumor is not uncommon and, depending on which type of treatment the patient initially received, autologous hematopoietic cell transplantation (HCT) may be an option. For patients who receive high-dose chemotherapy and autologous HCT for recurrent embryonal tumors, objective response is 50% to 75%; however, long-term disease control is obtained in fewer than 30% of patients and is primarily seen in patients in the first relapse with localized disease at the time of the relapse.1.

**Ependymoma**

Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. An ependymoma tumor typically arises intracranially in children, while in adults a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation.

**Other Central Nervous System Tumors**

Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. These tumors arise from glial cells, not neuroepithelial cells.

Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing sarcoma may be considered primitive neuroectodermal tumors. These peripheral tumors are considered in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Solid Tumors of Childhood.

**Hematopoietic Cell Transplantation**

HCT is a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone marrow ablative doses of cytotoxic drugs. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

**Hematopoietic Cell Transplantation for Brain Tumors**

Autologous HCT allows for escalation of chemotherapy doses above those limited by myeloablation and has been tried in patients with high-risk brain tumors in an attempt to eradicate residual tumor cells and improve cure rates. The use of allogeneic HCT for solid tumors does not rely on the escalation
of chemotherapy intensity and tumor reduction but rather on a graft-versus-tumor effect. Allogeneic HCT is not commonly used in solid tumors and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

**Literature Review**
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function- including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and 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.

**Central Nervous System Embryonal Tumors**

**Newly Diagnosed Central Nervous System Embryonal Tumors**

**Clinical Context and Therapy Purpose**
The purpose of autologous stem cell transplantation in patients who have newly diagnosed CNS embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does autologous stem cell transplantation used as treatment of newly diagnosed CNS embryonal tumors improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population(s) of interest are patients with newly diagnosed CNS embryonal tumors. CNS embryonal tumors are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term primitive neuroectodermal tumor (PNET); however, histologically similar tumors in different locations in the brain demonstrate different molecular genetic variants. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNET (sPNET), (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, atypical teratoid/rhabdoid tumor.

**Interventions**
The therapy being considered is autologous stem cell transplantation.

**Comparators**
The following practices are currently being used to make decisions about treatment of newly diagnosed CNS embryonal tumors: surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiotherapy because medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification as average- or high-risk. The average-risk group
includes children older than three years, without metastatic disease, and with tumors that are totally or near-totally resected (<1.5 cm² of residual disease). The high-risk group includes children aged three years or younger, or with metastatic disease, and/or subtotal resection (>1.5 cm² of residual disease).

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with a boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in 5-year overall survival (OS) rates of 80% or better. For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average event-free survival at 5 years ranges from 34% to 40% across studies. Fewer than 55% of children with the high-risk disease survive longer than 5 years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children younger than three years of age, because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and sometimes avoid the use of radiation and have included trials of higher dose chemotherapeutic regimens with autologous hematopoietic cell transplantation (HCT).

Supratentorial PNETs are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies. After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to 5-year overall survival (OS) rates of 40% to 50% have been reported, and, for patients with disseminated disease, survival rates at 5 years range from 10% to 30%.

Outcomes
The general outcomes of interest are OS, disease-specific survival (DSS), change in disease status, treatment-related mortality (TRM). Standard therapy for CNS embryonal tumors often involves craniospinal irradiation (CSI), in addition to surgical resection and chemotherapy. In pediatric patients, CSI is associated with impairments in neurodevelopmental outcomes, with risks increasing in younger age groups, particularly in those under the age of three. Research into pediatric CNS tumor treatments has yielded methods to reduce radiation exposure to the developing brain without conferring unacceptably high recurrence risks. Therefore, a relevant outcome in evaluating HCT for CNS embryonal tumors is whether the use of HCT allows radiation dose reduction.

Timing
Patients with newly diagnosed CNS embryonal tumors have been considered for stem cell transplantation in the setting of remission after induction therapy. If a transplant were to be performed follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Setting
Stem cell transplantation is performed in tertiary inpatient settings with specialized expertise.

Study Selection
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.
Observational Studies
The evidence describing outcomes after HCT for newly diagnosed CNS embryonal tumors consists of relatively small case series, some of which have enrolled patients prospectively. While most studies have reported outcomes for specific tumor types, several studies include multiple tumor types.

In a study that grouped CNS embryonal tumors, Odagiri et al (2014) reported outcomes for 24 patients treated for various CNS embryonal tumors on the basis of high- or average-risk prognosis. Among all patients included, 16, 4, 3, and 1, respectively, had medulloblastoma, PNET, atypical teratoid/rhabdoid tumor (AT/RT), and pineoblastoma. Nine patients were considered average-risk based on the presence of all of the following: age 3 years or older at diagnosis, nonmetastatic disease, and gross total resection; the remaining 16 patients were considered high-risk. High-risk patients received HCT in addition to CSI and chemotherapy. CSI for the high-risk group was at the same doses as for the average-risk group with nonmetastatic disease (23.4 gray [Gy] for those ≥5 years, 18 Gy for those <5 years old, with a boost of 54 Gy for all ages), with higher doses for those with metastatic disease (30-36 Gy, with a boost of 54 Gy). In the average-risk group (n=9), the 5-year progression-free survival (PFS) and OS rates were 71.1% and 88.9%, respectively. In the high-risk group (n=15), the 5-year PFS and OS rates were 66.7% and 71.1%, respectively. Survival rates did not differ significantly between the average- and high-risk groups.

Alsultan et al (2015) retrospectively reviewed outcomes for 10 children under age 3 years treated with HCT, with or without CSI, for CNS embryonal tumors. Of the ten patients, five had medulloblastoma, three had AT/RT, one had an embryonal tumor with abundant neuropil and true rosettes, and one had pineoblastoma; all underwent subtotal resection and induction chemotherapy. Five patients received radiotherapy, along with the AT/RT patient, who received radiotherapy as salvage therapy. The PFS rate was 50% (95% confidence interval [CI], 18% to 75%) at 1 year and at 2 years, with a median follow-up of 24 months. All patients with medulloblastoma were alive and without evidence of disease at last follow-up, including two with metastatic medulloblastoma who did not receive CSI.

Raleigh et al (2017) retrospectively described outcomes of 222 consecutive patients from institutional cancer registries at 2 California hospitals who had newly diagnosed embryonal brain tumors from 1988 to 2014. All patients underwent surgical resection. Following surgery, 56% of patients received adjuvant CSI followed by chemotherapy (upfront radiotherapy), 32% of patients received high-dose chemotherapy (HDC) with HCT to delay radiotherapy, and 16% received neither upfront radiotherapy nor HDC plus HCT due to death or poor clinical condition. Median follow-up was shorter in the HDC plus HCT group than in the upfront radiotherapy group (four years vs six years) and the mean age was younger (2.9 years vs 7.8 years). Time to initiation of radiotherapy was significantly longer in the HDC plus HCT group (median, 198 days) than in the upfront radiotherapy group (median, 28 days); moreover, 48% of HDC plus HCT patients did not receive radiotherapy. There were no differences in the incidence rates of metastases, PFS, or OS between HDC plus HCT and upfront radiotherapy.

Studies that describe HCT for specific tumor types are discussed next.

Supratentorial Primitive Neuroectodermal Tumor
Chintagumpala et al (2009) reviewed event-free survival (EFS) for 16 patients with newly diagnosed sPNET treated with risk-adapted CSI and subsequent HDC with autologous HCT between 1996 and 2003. Eight patients were considered at average-risk and eight at high-risk (defined as the presence of residual tumor >1.5 cm² or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range, 3-21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and OS rates for the patients with the average-risk disease were 75% and 88%, respectively, and for the high-risk patients 60% and 58%, respectively. No treatment-related toxicity deaths were reported. The authors concluded that HDC with HCT support after risk-adapted CSI permitted a reduction in the dose of radiation needed to treat nonmetastatic, average-risk sPNET, without compromising EFS.
Fangusaro et al (2008) reported on outcomes for 43 children with newly diagnosed sPNET treated prospectively in 2 serial studies (Head Start 1, Head Start 2) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HCT. There were no statistical differences between Head Start 1 and Head Start 2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was a partial response or complete response, patients underwent myeloablative chemotherapy with autologous HCT (n=32). Patients with progressive disease at the end of induction were ineligible for consolidation. Five-year EFS and OS rates were 39% (95% CI, 24% to 53%) and 49% (95% CI, 33% to 62%), respectively. Patients with nonpineal tumors did significantly better than patients with pineal PNETs (2- and 5-year EFS rates of 57% vs 23% and 48% vs 15%, respectively, and 2- and 5-year OS rates of 70% vs 31% and 60% vs 23%, respectively). Further, 60% of survivors were not exposed to radiotherapy.

Massimino et al (2013) reported on outcomes for 28 consecutive patients with noncerebellar PNET treated from 2000 to 2011 with an HDC schedule (methotrexate, etoposide, cyclophosphamide, carboplatin with or without vincristine) with autologous HCT rescue, followed by 1 of 2 radiotherapy options. For the first 15 patients, HDC and stem cell rescue was followed by hyperfractionated accelerated CSI with 2 high-dose thiotepa courses following CSI (for the first 15 patients); for subsequent cases, CSI was replaced with focal radiotherapy for patients whose tumors were nonmetastatic and not progressing during induction chemotherapy. Three- and 5-year PFS rates were 69% and 62%, respectively; 3- and 5-year EFS rates were 59% and 53%, respectively; and 3- and 5-year OS rates were 73% and 52%, respectively. Eleven children died at a median of 32 months after their diagnosis (range, 5-49 months), 8 due to their tumor, 1 due to multiorgan failure after the first myeloablative treatment, and 2 due to acute myeloid leukemia and myelodysplastic syndrome. For the 25 patients able to tolerate the entire schedule, including at least 1 myeloablative course, the 5-year PFS and OS rates were 67% and 61%, respectively.

Lester et al (2014) retrospectively evaluated the clinical outcomes and prognostic factors for 26 patients (11 children, 15 adults) with CNS PNET. Overall, 5-year disease-free survival rates were 78% for pediatric patients and 22% for adult patients (p=0.004); 5-year OS rates were 67% for pediatric patients and 33% for adult patients (p=0.07). More pediatric patients were treated with HDC plus HCT (82%) than adult patients (27%). In unadjusted analysis, compared with standard chemotherapy, treatment with HDC with HCT was associated with improved OS (hazard ratio, 0.3; 95% CI, 0.1 to 1.0; p=0.05). However, these results were confounded by higher rates of HCT use in children, who had better OS and disease-free survival.

Medulloblastoma

Dhall et al (2008) reported on outcomes for children younger than 3 years of age when diagnosed with nonmetastatic medulloblastoma, after being treated with 5 cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HCT. Twenty of the 21 children enrolled completed induction chemotherapy, of whom 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of seven patients with residual disease at the beginning of induction, all achieved a complete radiographic response to induction chemotherapy. Of the 20 patients who received consolidation chemotherapy, 18 remained disease-free at the end of consolidation. In patients with gross total tumor resection, 5-year EFS and OS rates were 64% and 79% respectively; for patients with residual tumor, 29% and 57% respectively. There were four treatment-related deaths. The need for CSI was eliminated in 52% of the patients, and 71% of survivors avoided irradiation completely while managing to preserve the quality of life and intellectual functioning.

Gajjar et al (2006) reported on the results of risk-adapted craniospinal radiotherapy followed by HDC and autologous HCT in 134 children with newly diagnosed medulloblastoma. After tumor resection, patients were classified as having average-risk disease (n=86), defined as 1.5 cm² or less of residual tumor and no metastatic disease, or high-risk disease (n=48), defined as greater than 1.5 cm² residual disease or metastatic disease localized to the neuroaxis. A total of 119 children
completed the planned protocol. The 5-year OS rate was 85% (95% CI, 75% to 94%) among the average-risk cases and 70% (95% CI, 54% to 84%) among the high-risk patients. The 5-year EFS rate was 83% (95% CI, 73% to 93%) and 70% (95% CI, 55% to 85%) for average- and high-risk patients, respectively. No treatment-related deaths were reported.

Bergthold et al (2014) reported on outcomes for 19 young children (age, <5 years) with classical or incompletely resected medulloblastoma treated with high-dose busulfan-thiotepa plus autologous HCT, followed by posterior fossa irradiation. Subjects were treated at a single-center from 1994 to 2010. On pathology, 14 patients had classic medulloblastoma, while three had desmoplastic/nodular medulloblastoma and one had medulloblastoma with extensive nodularity. Median follow-up was 40.5 months (range, 14.5-191.2 months). At 3 and 5 years, EFS and OS rates were 68% (95% CI, 45% to 84%) and 84% (95% CI, 61% to 94%), respectively. Treatment failures occurred in 6 children at a median of 13 months (range, 5.8-30.7 months) after HCT. Authors concluded that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

Atypical Teratoid/Rhabdoid Tumor
Lee et al (2012) retrospectively reviewed the medical records of 13 patients diagnosed with AT/RT who were treated at a children's hospital in South Korea. Median age was 12 months (range, 3-67 months), with 7 patients were younger than 1 year at diagnosis. Three (23%) patients underwent HDC and autologous HCT. Authors assessed the impact on OS in these three patients, as compared with the remaining ten patients who had other chemotherapy regimens. No statistical difference in OS was observed between these groups (p = 0.36); however, median survival was longer in the HCT group (15 months) than in the non-HCTs group (9 months).

Section Summary: Newly Diagnosed Central Nervous System Embryonal Tumors
Data evaluating HDC with autologous HCT in the setting of newly diagnosed CNS embryonal tumors is primarily from single-arm studies and case series. These studies have suggested comparable or improved EFS and OS rates compared with historical controls, particularly in patients with a disease considered high-risk. One retrospective study compared HDC with HCT and delayed CSI to upfront CSI. Rates of metastasis, PFS, and OS were similar in the two groups but patients in the delayed irradiation group were younger than those in the upfront irradiation group. HCT may permit reduced doses of CSI without worsening survival outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Recurrent or Relapsed Central Nervous System Embryonal Tumors
Clinical Context and Therapy Purpose
The purpose of autologous stem cell transplantation in patients who have recurrent or relapsed CNS embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does autologous stem cell transplantation used as treatment of recurrent or relapsed CNS embryonal tumors improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population(s) of interest are patients with newly diagnosed CNS embryonal tumors. CNS embryonal tumors are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term PNET; however, histologically similar tumors in different locations in the brain demonstrate different molecular genetic variants. Embryonal tumors of the CNS include medulloblastoma, medullopithelioma, sPNET (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, AT/RT. Recurrent childhood CNS embryonal tumor is not uncommon and, depending on which type of treatment the patient initially received, autologous HCT may be an
Interventions
The therapy being considered is autologous stem cell transplantation.

Comparators
The following practices are currently being used to make decisions about treatment of recurrent and relapsed CNS embryonal tumors: surgical resection should be attempted. Chemotherapy or radiation therapy alone or chemoradiation are additional treatment options. Some patients are candidates for palliative therapy.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, TRM.

Timing
Patients with recurrent or relapsed embryonal tumors have been considered for stem cell transplantation. If a transplant were to be performed, follow-up would be intensive weekly to monthly surveillance during the first year after transplant and lifelong if there is a successful transplant.

Setting
Stem cell transplantation is performed in tertiary inpatient settings with specialized expertise.

Study Selection
Methodologically credible studies were selected using the following principles:
   e. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
   f. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
   g. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
   h. Studies with duplicative or overlapping populations were excluded.

Observational Studies
Similar to the literature on HCT for newly diagnosed CNS embryonal tumors, the evidence on HCT for recurrent or relapsed CNS embryonal tumors consists of small series, most of which include patients with a single tumor type.

Relapsed Supratentorial Primitive Neuroectodermal
Raghuram et al (2012) reported on a systematic review of outcomes for patients with relapsed sPNET treated with HDC and autologous HCT. Eleven observational studies, including 4 prospective series (total n=46 patients) with relapsed sPNET or pineoblastoma, published before 2010, met reviewers’ inclusion criteria. Of the 46 patients, 15 were children younger than 3 years of age. After a median follow-up of 40 months (range, 3-123 months), 15 patients were reported alive. Of the 15 survivors, 13 did not receive CSI. For the entire cohort, OS was 44.2 months; OS was longer for children younger than 36 months (66.7 months) than for those over 36 months (27.8 months; p=0.003). In multivariable regression, pineal location was the only independent adverse prognostic factor for survival. Based on these pooled results, CSI may not be associated with survival outcomes in young children treated with HCT. However, OS is poor in older children with relapsed sPNET, particularly with pineal tumors, even when treated with HCT.
Relapsed Medulloblastoma
Dunkel et al (2010) reported on an expanded series with longer follow-up using autologous HCT for previously irradiated recurrent medulloblastoma.\textsuperscript{15} Twenty-five patients (18 males, 7 females) were treated between 1990 and 1999 and had a median age at diagnosis of 11.5 years (range, 4.2-35.5 years). Median age at the time of HCT was 13.8 years (range, 7.6-44.7 years). All patients had previously received postoperative external-beam radiotherapy with (n=15) or without (n=10) chemotherapy. Median time from diagnosis to disease relapse or progression was 29.8 months (range, 5.3-114.7 months). The stage at relapse was M0 (n=6), M1 (n=1), M2 (n=8), and M3 (n=10) (M0=no evidence of subarachnoid or hematogenous metastasis, M1=tumor cells found in cerebrospinal fluid, M2=intracranial tumor beyond primary site, M3=gross nodular seeding in spinal subarachnoid space). HDC before HCT consisted of carboplatin, thiotepa, and etoposide. TRM was 12% within 30 days of transplant. Tumors recurred in 16 patients at a median of 8.5 months after HCT (range, 2.3-58.5 months). Median OS was 26.8 months (95% CI, 11.9 to 51.1 months) and EFS and OS rates at 10 years post-HCT were 24% for both (95% CI, 9.8% to 41.7%). Authors concluded that this retrieval strategy provided “long-term EFS for some patients with previously irradiated recurrent medulloblastoma.”

In the earlier publication, Dunkel et al (1998) reported on outcomes for 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiotepa, and etoposide.\textsuperscript{16} Seven patients were event-free survivors at a median of 54 months, with the OS rate estimated at 46% at 36 months. HCT was expected to be most effective with minimal disease burden. Thus, Dunkel et al (1998) suggested increased surveillance for recurrence or aggressive surgical debulking at the time of recurrence. They also acknowledged the potential for selection bias to influence their results because not all patients eligible for the protocol were enrolled.

Grodman et al (2009) reported on outcomes for 8 patients with relapsed medulloblastoma with metastasis (n=7) and relapsed germinoma (n=1) who received dose-intensive chemotherapy with autologous HCT.\textsuperscript{17} Mean age was 12.9 years (range, 5-27.8 years). Mean survival posttransplant was 4.8 years (range, 8-160+ months). Two-year and 5-year OS rates were 75% and 50%, respectively.

Kostaras et al (2013) conducted a systematic review of therapies for adults with relapsed medulloblastoma, including HDC with HCT.\textsuperscript{18} Reviewers identified 13 publications including 66 adults treated with HCT for recurrent or relapsed medulloblastoma. Limitations of the selected studies included the fact that all were small case series, case reports, or retrospective reviews. The single study with a comparator group identified in the review, which included ten patients treated with HCT, reported that patients with medulloblastoma treated with HDC plus HCT at recurrence had improved OS (3.47 years) compared with historical controls treated with conventional chemotherapy at recurrence (two years; p=0.04). Reviewers concluded: “Although the data are limited, the collective published evidence for this treatment modality suggests a role for HDCT [high-dose chemotherapy] plus stem cell transplantation in the management of well-selected adult patients with recurrent medulloblastoma.”

Relapsed Embryonal Tumors: Multiple Types
The largest study identified an HCT in relapsed CNS embryonal tumors included patients with multiple PNET types (medulloblastoma, sPNET). Bode et al (2014) reported on the results of the intensive chemotherapy treatment arm of a nonrandomized stratified protocol for the treatment of relapsed cerebral PNET, in which patients could receive intensive chemotherapy, which could be potentially high-dose or oral chemotherapy.\textsuperscript{19} The intensive chemotherapy arm included 72 patients, 59 of whom had disseminated disease. Patients in the intensive treatment arm received conventional chemotherapy with carboplatin and etoposide; those considered to have a good response underwent HCT. At the end of conventional intravenous and/or intrathecal chemotherapy, 34 (48%) patients were considered to be good responders, of whom 24 were selected for HCT, along with 3 patients with stable disease. Among the 72 patients who received intensive chemotherapy, median PFS was 11.6 months (95% CI, 10.1 to 13.1 months), with 2-, 3-, and 5-year PFS rates of 44%, 18%, and 0.5%, respectively. Among all patients, median OS was 21.9 months (95% CI, 15.7 to 26.5 months), with
2-, 3-, and 5-year OS rates of 45%, 31%, and 16%, respectively. Among those treated with HCT, median PFS was 8.4 months (95% CI, 7.7 to 9.1 months), with 2-, 3-, and 5-year PFS rates of 20%, 10%, and 0.1%, respectively. HCT-treated patients had median OS of 20.2 months (95% CI, 11.7 to 28.8 months), with 2-, 3-, and 5-year OS rates of 35%, 30%, and 17% respectively. Among the 34 good responders, there was no difference in OS or PFS between those treated with and without HCT.

Gill et al (2008) reported on outcomes for 23 adults (≥18 years of age) treated for recurrent embryonal CNS tumors between 1976 and 2004, comparing HDC plus autologous HCT (n=10) with a historical control group of patients treated with conventional-dose chemotherapy (n=13). In the HCT group, six patients received tandem autologous transplants. Autologous HCT was associated with increased survival (p=0.044) and a longer time to progression of disease (p=0.028). Median time to progression for the conventional chemotherapy vs HCT was 0.58 years and 1.25 years, respectively. Median survival was 2.00 years and 3.47 years, respectively. There were no long-term survivors in the conventional chemotherapy group. With a median follow-up of 2.9 years, five of the HCT patients were alive, four without disease progression. In a comparison of outcomes between patients who received a single vs tandem transplant, there was an improvement in time to progression favoring tandem transplant (p=0.046), but no difference in survival was observed (p=0.132).

Kim et al (2013) reported on outcomes for 13 patients with refractory or relapsed medulloblastoma or PNET treated with combination HDC, with an objective tumor response rate of 38.5%. However, while the authors noted that patients could concurrently receive radiotherapy, surgery, and/or HDC and stem cell rescue, they did not specify how many patients received stem cell support, making it difficult to determine the benefit from specific intervention components.

Egan et al (2016) reported on outcomes from a phase 1 study of temozolomide in combination with thiotepa and carboplatin plus autologous HCT in patients with recurrent malignant brain tumors. Temozolomide was administered, followed by thiotepa and carboplatin and then autologous HCT. The study enrolled 27 patients (age range, 3-46 years) with high-grade glioma (n=12), medulloblastoma/PNET (n=9), CNS germ cell tumor (n=4), ependymoma (n=1), and spinal cord PNET (n=1). Fourteen (52%) patients survived longer than 24 months. After ten years, three patients were alive.

Section Summary: Recurrent or Relapsed Central Nervous System Embryonal Tumors
The prognosis is generally poor for recurrent CNS tumors, and there are few treatment options. Data from some single-arm studies using autologous HCT compared with conventional therapy to treat recurrent CNS embryonal tumors have shown comparable or improved survival for certain patients. A 2012 systematic review of observational studies in patients with relapsed sPNET suggested that infants with the chemosensitive disease might benefit from autologous HCT because survival outcomes are similar without radiotherapy. However, reviewers found that outcomes in older children and/or in those with the pineal location were poor with this modality. A relatively large prospective multicenter study reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Central Nervous System Embryonal Tumors Treated with Tandem Transplant
Clinical Context and Therapy Purpose
The purpose of tandem autologous stem cell transplantation in patients who have CNS embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does tandem autologous stem cell transplantation used as a treatment of CNS embryonal tumors improve net health outcomes?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population(s) of interest are patients with CNS embryonal tumors.

Interventions
The therapy being considered is tandem autologous HCT which has been investigated as a therapy in the setting of remission after induction therapy. A tandem transplant may include a dose escalation of the conditioning chemotherapy regimen.

Comparators
The following practices are currently being used to make decisions about treatment of CNS embryonal tumors: chemotherapy or chemoradiation.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, TRM.

Timing
Patients with CNS embryonal tumors have been considered for stem cell transplantation in the setting of remission after induction therapy or relapse after first-line chemotherapy. If a transplant were to be performed follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Setting
Stem cell transplantation is performed in tertiary inpatient settings with specialized expertise.

Study Selection
Methodologically credible studies were selected using the following principles:

i. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

j. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

k. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

l. Studies with duplicative or overlapping populations were excluded.

Observational Studies
Sung et al (2016) reported on prospective follow-up for 13 children with AT/RT who received tandem HDC and autologous HCT.23 Five of the children were less than three years old; the remaining eight were three years or older. Tandem HDC and autologous HCT were administered after six cycles of induction chemotherapy with radiotherapy deferred until age three unless the tumor showed relapse or progression in the younger children. Reduced-dose radiotherapy was administered either after two cycles of induction chemotherapy or after surgery with tandem HDC, and autologous HCT was performed after six cycles of induction chemotherapy in the older children. All five younger children died from disease progression. Four of the 8 older children remained progression-free, with a median follow-up of 64 months.

Dufour et al (2014) reported on outcomes for patients with newly diagnosed high-risk medulloblastoma and sPNET treated with tandem HDC and autologous HCT support followed by conventional craniospinal radiotherapy.24 Twenty-four children older than age 5 years were treated from 2001 to 2010, 21 with newly diagnosed high-risk medulloblastoma (disseminated medulloblastoma or medulloblastoma with residual tumor volume >1.5 cm² or MYCN amplification) and three with sPNET. Patients received two courses of conventional chemotherapy, followed by two courses of high-dose thiotepa followed by stem cell rescue and craniospinal radiotherapy. Twenty-three patients received two courses of HDC, while one patient received only one course of high-dose thiotepa due to seizures. Median follow-up was 4.4 years (range, 0.8-11.3 years). Three-year EFS and OS rates were 79% (95% CI, 59% to 91%) and 82% (95% CI, 62% to 93%), respectively,
while 5-year EFS and OS rates were 65% (95% CI, 45% to 81%) and 74% (95% CI, 51% to 89%), respectively.

Sung et al (2013) reported on the results of reduced-dose craniospinal radiotherapy followed by double-tandem HDC with autologous HCT in 20 children older than 3 years of age with high-risk medulloblastoma (17 with metastatic disease, 3 with postoperative residual tumor >1.5 cm² without metastasis). The tumor relapsed or progressed in four patients, and two died of treatment-related toxicity during the second transplant. Fourteen (70%) patients remained event-free at a median follow-up of 46 months (range, 23-82 months) from diagnosis. Late adverse events, evaluated at a median of 36 months (range, 12-68 months) after tandem HCT included hypothyroidism, growth hormone deficiency, sex hormone deficiency, hearing loss, and renal tubulopathy.

Friedrich et al (2013) reported on the results of double-tandem HDC with autologous HCT in 3 children younger than 4 years of age with metastatic sPNET. These patients also received preventive craniospinal radiotherapy; they had the residual disease before HCT, but no evidence of disease after transplant (survival range, 2-10 years).

Park et al (2012) reported on the results of double-tandem HDC with autologous HCT in 6 children younger than 3 years of age with newly diagnosed AT/RT. No treatment-related death occurred during the tandem procedure, and 5 (of 6) patients were alive at a median follow-up of 13 months (range, 7-64 months) from the first transplant. Although three patients remained progression-free after tandem HCT, the effectiveness of this modality is unclear because all survivors received radiotherapy and tandem HCT.

Sung et al (2007) reported on the results of a single- or double-tandem HDC with autologous HCT in 25 children with newly diagnosed high-risk or relapsed medulloblastoma or PNET following surgical resection. Three-year EFS rates for patients in complete or partial response and less than partial response at first HDC were 67% and 16.7%, respectively. For 19 cases in complete or partial response at first HDC, 3-year EFS rates were 89% in the double-tandem group and 44% in the single HDC group, respectively. Four treatment-related deaths occurred, and in four of eight young children, craniospinal radiotherapy was successfully withheld without relapse.

**Section Summary: Central Nervous System Embryonal Tumors Treated with Tandem Transplant**

Little evidence is available on the use of tandem autologous HCT for CNS embryonal tumors. The single-arm studies are very small but appear to report OS and EFS rates comparable with single autologous HCT. Tandem transplants may allow reduced doses of craniospinal irradiation, but most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Central Nervous System Embryonal Tumors Treated with Allogeneic Transplant**

Use of allogeneic HCT for CNS embryonal tumors consists of rare case reports with mixed results.

**Central Nervous System Ependymoma Tumors Treated with Autologous Transplant**

**Clinical Context and Therapy Purpose**

The purpose of autologous stem cell transplantation in patients who have CNS ependymomas is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does autologous stem cell transplantation used as treatment of CNS ependymomas improve net health outcomes?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population(s) of interest are patients with CNS ependymomas. Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. An ependymoma tumor typically arises intracranially in children, while in adults a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation.

Interventions
The therapy being considered is autologous stem cell transplantation. Treatment of recurrence is problematic; further surgical resection or radiotherapy is usually not possible. Given the poor response to conventional-dose chemotherapy, HDC with autologous HCT has been investigated as possible salvage therapy.

Comparators
The following practices are currently being used to make decisions about treatment of ependymomas. Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy usually does not play a role in the initial treatment of ependymoma. However, disease relapse is common, typically occurring at the site of origin.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, TRM.

Timing
Patients with CNS ependymoma have been considered for stem cell transplantation in the setting of recurrence after first-line therapy. If a transplant were to be performed follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Setting
Stem cell transplantation is performed in tertiary inpatient settings with specialized expertise.

Study Selection
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies
The literature on autologous HCT for the treatment of ependymoma primarily consists of small case series. Sung et al (2012) reported the results of double-tandem HDC with autologous HCT in 5 children younger than 3 years of age with newly diagnosed anaplastic ependymoma. All patients were alive at median follow-up of 45 months (range, 31-62 months) from diagnosis, although the tumor progressed at the primary site in 1 patient. No significant endocrine dysfunction occurred except for hypothyroidism in one patient, and significant neurologic injury from primary surgical treatment in another patient. The results of this very small case series indicate that treatment with tandem HCT is feasible in very young children with anaplastic ependymoma and that this strategy might also be an option to improve survival in these patients without unacceptable long-term toxicity.

Mason et al (1998) reported on a case series of 15 patients with recurrent ependymoma. Five patients died of treatment-related toxicities, eight died from progressive disease, and one died of...
unrelated causes. After 25 months, 1 patient remained alive but with tumor recurrence. Authors concluded that their high-dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill et al (1996) similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen.34.

A small 2007 series reported 5-year EFS and OS rates of 12% and 38%, respectively, among 29 children younger than 10 years of age who received autologous HCT after intensive induction chemotherapy to treat newly diagnosed ependymoma.35 Importantly, the radiation-free survival rate was only 8% in these cases. The results of these series, although limited in size, would suggest HCT is not superior to other previously reported chemotherapeutic approaches.

Section Summary: CNS Ependymomas Treated with Autologous Stem Cell Transplant
For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. The relevant outcomes are OS, DSS, and TRM and morbidity. The available case series do not report higher survival rates for patients with ependymoma treated with HCT compared with standard therapies. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Summary of Evidence
For individuals who have newly diagnosed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective studies. The relevant outcomes are OS, DSS, and TRM and morbidity. For pediatric CNS embryonal tumors, an important consideration is whether the use of HCT may allow for a reduction in radiation dose. Data from single-arm studies using HDC with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both EFS and OS) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with a disease considered high-risk. In a retrospective comparative study, survival in patients receiving HDC with HCT and delayed craniospinal irradiation was comparable with survival in those receiving upfront craniospinal irradiation. Overall, data from these observational studies have suggested HCT may allow reduced doses of craniospinal irradiation without worsening survival outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent or relapsed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective single-arm studies and a systematic review of these studies. The relevant outcomes are OS, DSS, and TRM and morbidity. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT vary, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HCT to treat recurrent CNS embryonal tumors have shown comparable or improved survival compared with historical controls treated with conventional therapy for certain patients. The results of a 2012 systematic review of observational studies in patients with relapsed supratentorial embryonal tumors suggested that a subgroup of infants with the chemosensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas outcomes in older children and/or in pineal location are poor with this modality. However, a relatively large prospective multicenter study has reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy. Overall, data from these single-arm studies have suggested HCT may be associated with improved survival outcomes in select patients, although data for some tumor types are limited (e.g., atypical teratoid/rhabdoid tumors). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CNS embryonal tumors who receive tandem autologous HCT, the evidence includes prospective and retrospective single-arm studies. Less evidence specifically addresses the use of tandem autologous HCT for CNS embryonal tumors. The available single-arm studies are very small but appear to report OS and EFS rates comparable with single autologous HCT. Tandem transplants might allow reduced doses of craniospinal irradiation, with the goal of avoiding long-term radiation damage. However, most
studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNS embryonal tumors who receive allogeneic HCT, the evidence includes case reports. The relevant outcomes are OS, DSS, and TRM and morbidity. The available evidence is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. The relevant outcomes are OS, DSS, and TRM and morbidity. The available case series do not report higher survival rates for patients with ependymoma treated with HCT compared with standard therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines on treating central nervous system tumors (v.2.2018) make the following recommendations about hematopoietic cell transplant (HCT):

- For medulloblastoma and supratentorial primitive neuroectodermal tumor, autologous HCT for localized recurrent disease with maximum safe resection is a category 2A recommendation.

American Society for Blood and Marrow Transplantation
The American Society for Blood and Marrow Transplantation (2015) published consensus guidelines on the use of HCT to treat specific conditions, in both clinical trial and clinical practice settings. Per this review, clinical evidence is available to support autologous HCT in pediatric patients (<18 years) with medulloblastoma. Stem cell transplantation is not generally recommended using allogeneic HCT for medulloblastomas. The guidelines did not address HCT in treating ependymomas.

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 1.

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<th>NCT No.</th>
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<td>A Multi-Institutional Phase II Feasibility Study of Allogeneic Hematopoietic Stem Cell Transplantation for Patients With Malignant Neuro-Epithelial and Other Solid Tumors</td>
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<td>96</td>
<td>Dec 2016 (completed)</td>
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NCT: national clinical trial.

References


**Documentation for Clinical Review**

Please provide the following documentation (if when requested):

- Referring physician history and physical
- Stem Cell 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 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.

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Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

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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.

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<td>04/01/2016</td>
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<td>01/01/2018</td>
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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 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.