

## Corporate Medical Policy

### Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

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<b>Origination:</b>	2/2001
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#### Description of Procedure or Service

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High-dose chemotherapy with hematopoietic stem cell transplantation (HSCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in patients with disease that is considered high-risk. In addition, the use of HSCT has allowed for a reduction in the dose of radiation needed to treat both average and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival.

#### **Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs. Bone-marrow stem cells may be obtained from the transplant recipient (i.e., autologous HSCT) or from a donor (i.e., allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

#### **Hematopoietic Stem-Cell Transplantation for Brain Tumors**

Autologous HSCT 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 HSCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction, but rather on a graft-versus-tumor (GVT) effect. Allogeneic HSCT is not commonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

#### **CNS Embryonal Tumors**

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system (CNS) embryonal tumors are more common in children and are the most common brain tumor in childhood. 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 alterations. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNETs (pineoblastoma, cerebral neuroblastoma, and ganglioneuroblastoma), ependymblastoma, and atypical teratoid/rhabdoid tumor (AT/RT).

# Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison. Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiation therapy, as medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification, as average or high risk. The average-risk group includes children older than 3 years, without metastatic disease, and with tumors that are totally or near totally resected (<1.5 cm<sup>2</sup> of residual disease). The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (>1.5 cm<sup>2</sup> of residual disease).

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with 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%–40% across studies. Fewer than 55% of children with high-risk disease survive longer than 5 years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children under the age of 3 years, 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 HSCT.

Supratentorial PNETs (sPNET) 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 OS rates of 40%–50% have been reported, and for patients with disseminated disease, survival rates at 5 years range from 10%–30%.

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

## 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 ependymblastomas due to their more mature histologic differentiation. 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. Treatment of recurrence is problematic; further surgical resection or radiation therapy is usually not possible. Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy with autologous HSCT has been investigated as a possible salvage therapy.

**Note:** Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. However, these tumors arise from glial cells and not neuroepithelial cells.

**Note:** Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing's sarcoma may be considered PNETs. However, these peripheral tumors are considered separately in policy entitled, Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

# Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

*\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

## Policy

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**BCBSNC will provide coverage for hematopoietic stem-cell transplantation for embryonal tumors of the CNS when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

**Hematopoietic stem-cell transplantation for ependymoma is considered investigational for all indications. BCBSNC does not cover investigational services or procedures.**

**If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**Some health benefit plans may exclude benefits for transplantation.**

## When Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma are covered

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### Embryonal tumors of the CNS

Autologous hematopoietic stem-cell transplantation may be considered **medically necessary** 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).

Autologous hematopoietic stem-cell transplantation may be considered **medically necessary** to treat recurrent embryonal tumors of the CNS.

## When Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma are not covered

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### Embryonal tumors of the CNS

- Allogeneic hematopoietic stem-cell transplantation is **investigational** to treat embryonal tumors of the CNS.
- Tandem autologous hematopoietic stem-cell transplant is **investigational** to treat embryonal tumors of the CNS.

### Ependymoma

# Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

- Autologous, tandem autologous and allogeneic hematopoietic stem-cell transplant is **investigational** to treat ependymoma.

## Policy Guidelines

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Refer to the individual member's benefit booklet for prior review requirements.

For individuals who have newly diagnosed central nervous system (CNS) embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. In the case of 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 event-free survival and overall survival) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with disease that is considered high risk. In a retrospective comparative study, survival in patients receiving HDC with HCT and delayed craniospinal irradiation was comparable to survival in those receiving upfront craniospinal irradiation. Overall, data from these observational studies has 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/relapsed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective single-arm studies and a systematic review of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT are variable, 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 primitive neuroectodermal tumor (sPNET) suggested that a subgroup of infants with 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 has suggested HCT may be associated with improved survival outcomes in select patients, although data for some tumor types is limited (eg, 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. Relevant outcomes are overall survival, disease specific survival, and treatment-related morbidity and mortality. 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 overall survival and event-free survival rates comparable to single autologous HCT. Tandem transplants may 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. Relevant outcomes are overall survival, disease-specific survival, and treatment-related

# Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

morbidity and mortality. 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. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available case series do not report higher survival rates for patients with ependymoma treated with HCT than with standard therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## **Scientific Background and Reference Sources**

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### **Bone Marrow Transplant for Neuroectodermal Tumors and Ependymoma**

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Dunkel IJ, Boyett JM, Yates A, Rosenblum M, Garvin JH Jr., Bostrom BC, Goldman S, Sender LS, Gardner SL, Li H, Allen JC, Finlay JL. High dose carboplatin, thiotepa, and etoposide with autologous stem cell rescue for patients with recurrent medulloblastoma. *Children's Cancer Group. Journal of Clinical Oncology*, Jan, 1998; 16:222-228.

Mason WP, Goldman S, Yates AJ, Boyett J, Li H, Finlay JL, Memorial Sloan Kettering Cancer Center, New York, New York, USA. Survival following intensive chemotherapy with bone marrow reconstitution for children with recurrent intracranial ependymoma. A report of the Children's Cancer Group. *Journal of Neuro-Oncology*, April 1998; 37:133-143.

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 9/27/2005

Specialty Matched Consultant Advisory Panel - 11/2006

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 5/8/2008

Specialty Matched Consultant Advisory Panel - 11/2008

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Medical Director – 9/2010

Specialty Matched Consultant Advisory Panel – 11/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 11/11/2010

Specialty Matched Consultant Advisory Panel – 11/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 11/10/2011

Specialty Matched Consultant Advisory Panel – 12/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 11/8/2012

Specialty Matched Consultant Advisory Panel – 11/2013

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 1/14/2016

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 1/17/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.28, 1/17/2019

Specialty Matched Consultant Advisory Panel – 11/2019

## **Policy Implementation/Update Information**

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### **Bone Marrow Transplant for Neuroectodermal Tumors and Ependymoma**

- 1/01 Specialty Matched Consultant Advisory Group.
- 2/01 Original policy issued.
- 2/03 Specialty Matched Consultant Advisory Panel review 11/2002. Revised first paragraph under when it is not covered to include, "or to consolidate a complete remission after initial therapy for medulloblastoma and other PNET's of the CNS. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.
- 1/04 Benefits Application and Billing/Coding sections updated for consistency.
- 2/04 Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.
- 7/29/04 HCPCS code S2150 added to Billing/Coding section.
- 12/23/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. No changes to criteria. Revised Description of Procedure or Service. Added policy statement specific to ependymoma in Policy section. Revised wording in When not covered section. Added additional information to Policy Guidelines section regarding "residual tumor". Added rationale to Policy Guidelines section. Added policy number to Policy Key Words section. "Hematopoietic" and "Opportunistic" added to Definitions. References added.
- 12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/2006. Added the following statement to the "Policy" section; "If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services for Life-Threatening Conditions." Changed the wording in the "When Covered" section from "refractory" to "residual". Updated "Policy Guidelines" section. References added.

# Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

## **Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma**

- 10/26/10 Policy name changed from “Bone Marrow Transplant for Neuroectodermal Tumors and Ependymoma” to “Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma”. “Description” section entirely revised. Removed the statement in the “Benefit Application” section that indicated “Services for or related to the search for a donor are not covered.” Removed reference to "Bone Marrow Transplant, high dose chemotherapy and stem cell support" and inserted "hematopoietic stem-cell transplantation" throughout policy as appropriate. Changed wording in the “When Covered” section to indicate; “Autologous hematopoietic stem-cell transplantation may be considered medically necessary 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). Autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat recurrent embryonal tumors of the CNS.” Revised the “When Not Covered” section to indicate; “Allogeneic hematopoietic stem-cell transplantation is investigational to treat embryonal tumors of the CNS. Tandem autologous hematopoietic stem-cell transplant is investigational to treat embryonal tumors of the CNS.” No change to policy intent. “Policy Guidelines” section updated. References added. Reviewed by Medical Director 9/27/10. (btw)
- 1/4/11 Specialty Matched Consultant Advisory Panel review 11/29/2010. No changes to policy. (btw)
- 1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/2011. No changes to policy. (btw)
- 2/7/12 Added new 2012 CPT code, 38232 to Billing/Coding section. Reference added. (btw)
- 1/15/13 Specialty Matched Consultant Advisory Panel review 12/4/2012. No change to policy intent. Added new 2013 CPT code, 38243 to Billing/Coding section. Reference added. Description and Policy Guidelines sections updated. Medical Director review 12/18/2012. (btw)
- 12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. Policy Guidelines updated. No change to policy intent. (btw)
- 2/11/14 Minor updates to the Description and Policy Guidelines sections. No change to policy intent. Reference added. (btw)
- 12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. Reference added. (lpr)
- 12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)
- 4/1/16 Updated Policy Guidelines section. No change to policy intent. Reference added. (lpr)
- 12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

# Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

- 2/24/17 Revised Policy Guidelines section. Reference added. No change to policy intent. (lpr)
- 12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)
- 1/15/19 Specialty Matched Consultant Advisory Panel review 11/2018. Reference added. No change to policy statement. (lpr)
- 12/31/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. References added. No change to policy statement. (lpr)

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