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Policy Effective Date	**07/15/2024**
Policy End Date	**12/31/2025**

Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas

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Related Policies (if applicable)
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Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Hematopoietic cell transplantation **is considered experimental, investigational and/or unproven** as a treatment of malignant astrocytomas and gliomas, including both glioblastoma multiforme and oligodendroglioma.

Policy Guidelines

None.

Description

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic 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. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Preparative Conditioning for Hematopoietic Stem Cell Transplantation
Autologous HCT necessitates myeloablative chemotherapy to eradicate cancerous cells from the blood and bone marrow, thus permitting subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic progenitor cells. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment but not graft-versus-host disease.

Astrocytomas and Gliomas
Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into 3 grades of malignancy: grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme. Oligodendrogliomas are diffuse neoplasms that are clinically and biologically most closely related to diffuse fibrillary astrocytomas. However, these tumors generally have better prognoses than diffuse

astrocytomas, with mean survival times of 10 years versus 2–3 years, respectively. In addition, oligodendrogliomas appear to be more chemosensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than 2 years for most patients.

Treatment of primary brain tumors focuses on surgery, either with curative intent or optimal tumor debulking. Surgery may be followed by radiation therapy and/or chemotherapy. Survival after chemoradiotherapy is largely dependent on the extent of residual tumor after surgical debulking. Therefore, tumors that arise in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex, which typically cannot be extensively resected, have a particularly poor outcome. Treatment of children younger than 3 years is complicated by the long-term effects of radiation therapy on physical and intellectual function. Therefore, in young children, radiation of the central nervous system (CNS) is avoided whenever possible.

NOTE 2: Astrocytomas and gliomas arise from the glial cells. Tumors arising from the neuroepithelium constitute a separate category of malignancies that include CNS neuroblastoma, medulloblastoma, ependymoblastomas, and pineoblastomas. Collectively these tumors may be referred to as primitive neuroectodermal tumors (PNETs). Ependymomas also arise from the neuroepithelium, but because of their more mature histologic appearance, they are not considered a member of the PNET family. The use of high-dose chemotherapy in tumors arising from the neuroepithelium is addressed separately in Medical Policy SUR703.039.

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

Rationale

High-dose chemotherapy (HDC) followed by hematopoietic cell transplant (HCT) (i.e., blood or marrow) is an effective treatment modality for many patients with certain malignancies and non-malignancies. The rationale of this treatment approach is to provide a very dose-intensive treatment in order to eradicate malignant cells followed by rescue with peripheral blood, bone marrow, or umbilical cord blood stem cells.

The literature search of the PubMed database for this medical policy was conducted through April 5, 2022. The following is a summary of the key literature to date.

Astrocytomas
A nonrandomized study compared survival outcomes of 27 children (age 0.4–22 years) with recurrent malignant astrocytomas who underwent myeloablative chemotherapy and

autologous HCT with outcomes in a matched historical cohort (n=56) that received standard chemotherapy regimens following tumor recurrence. (1) Among the 27 children who received myeloablative chemotherapy and autologous HCT, 5 (18%) succumbed to treatment-related toxicities within approximately 2 months of transplantation, 17 (63%) had disease progression, while 5 survived and were alive a median of 11 years (range: 8–13 years) after transplantation. Overall survival (OS) rates at 4 years were 40 ± 14% for transplant patients versus 7 ± 4% with conventional chemotherapy (p=0.018, hazard ratio [HR]: 1.9; 95% confidence interval [CI]: 1.1–3.2). The results of this study suggest myeloablative chemotherapy with autologous HCT can produce long-term survival among children with recurrent malignant astrocytoma. However, lack of a contemporaneous treatment comparison group precludes conclusions as to the relative efficacy of this approach.

A 2012 comprehensive review article identified in the literature search did not report any evidence for the role of HCT in this disease. (2)

Gliomas

Bouffet et al. reported on a series of 22 children and young adults with high-grade gliomas treated with autologous HCT. (3) The response rate was 29% with one complete and three partial responses. However, the authors concluded that survival with this procedure was no better than that reported with conventional treatments. Heideman et al. reported on a case series of 13 pediatric patients with bulky disease or recurrent disease treated with HCT plus radiotherapy. (4) While the overall response rate was 31%, the authors similarly concluded that overall survival was no better than conventional treatment regimens. Finlay et al. reported on a 1996 case series of 45 children and young adults with a variety of recurrent CNS tumors, including gliomas, medulloblastomas, ependymomas, and primitive neuroectodermal tumors. (5) Of the 18 patients with high-grade gliomas, the response rate was 29%. The median survival of this group was 12.7 months. Of the five long-term survivors, all had high-grade glioma with minimal residual disease at the time of transplantation. Based in part on these results, the authors recommended aggressive surgical debulking before this procedure is even considered. Studies focusing on the use of autologous HCT in adults with glioblastoma multiforme reported results similar to those in children, being most successful in those with minimal disease at the time of treatment, with an occasional long-term survivor. (6, 7)

A review by Brandes et al. concluded that the high drug doses used in this treatment caused excessive toxicity that was not balanced by a significant improvement in survival. (8) Additional reports on small, uncontrolled series of patients with pontine gliomas (9), recurrent oligodendrogliomas, (10) or those undergoing radiation therapies for high-grade gliomas (11) also did not suggest that this treatment improves survival. In a 2006 Phase II study, Abrey et al. (12) evaluated hematopoietic stem cell transplantation in 39 patients with newly diagnosed oligodendroglioma. The authors reported the median follow-up of surviving patients was 80.5 months and with 78 months progression-free survival. The OS median had not been reached and 18 patients (46%) had relapsed.

Recent studies on autologous HCT are limited. However, one study was published by Egan et al. reporting on a specific HDC regimen followed by autologous HCT for patients with a recurrence of malignant brain tumors. (13) Twenty-seven patients aged 3-46 years were enrolled. Diagnoses included high-grade glioma (n=12); medulloblastoma/primitive neuro-ectodermal tumor (PNET) (n=9); central nervous system (CNS) germ cell tumor (n=4); ependymoma (n=1); and spinal cord PNET (n=1). Prolonged survival (life expectancy of >3 months) was noted in several patients including those with recurrent high-grade glioma, medulloblastoma, and CNS germ cell tumor. The authors concluded continued study is needed, particularly for the chemotherapy regimen.

Osorio et al. (2018) investigated the role of intensive, including marrow-ablative, chemotherapy regimens in the treatment of young children with newly-diagnosed, high-grade brainstem glioma (BSG). (14) Between 1991 and 2002, 15 eligible children less than 10 years of age with a diagnosis of high-grade BSG, were treated on "Head-Start" I and II protocols (HSI and HSII). Treatment included induction with 4-5 cycles of one of three intensive chemotherapy regimens followed by consolidation with one cycle of marrow-ablative chemotherapy (thiotepa, carboplatin, and etoposide) with autologous hematopoietic cell rescue (AHCR). Irradiation was required for children over 6 years of age or for those with residual tumor at the end of consolidation. Two long-term survivors were found retrospectively to harbor low-grade glial tumors and thus were not included in the survival analysis. Of the remaining 13 patients, the 1-year event-free (EFS) and OS for these children were 31% (95% CI 9-55%) and 38% (95% CI 14-63%), respectively. Median EFS and OS were 6.6 (95% CI 2.7, 12.7) and 8.7 months (95% CI 6.9, 20.9), respectively. Eight patients developed progressive disease during study treatment; seven during Induction and one at the end of consolidation. Ten children received focal irradiation, five for residual tumor (three following induction and two following consolidation) and five due to disease progression. Authors concluded that children with high-grade BSG did not benefit from this intensive chemotherapy strategy administered prior to irradiation.

Summary of Evidence

The data on the use of hematopoietic cell transplantation (HCT) for malignant astrocytomas and gliomas has, in general, shown no survival benefit compared to conventional therapy with increased treatment-related toxicity. One small study emerged, with several more ongoing that may show some benefit. However, additional studies are warranted to demonstrate positive outcomes of astrocytomas and gliomas following autologous HCT. Therefore, HCT is considered experimental, investigational and/or unproven for the treatment of malignant astrocytomas and gliomas, which includes both glioblastoma multiforme and oligodendroglioma.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines:

The 2024 NCCN Guidelines on Central Nervous System Tumors (v1.2024) do not list HCT as a treatment option for patients with astrocytomas or gliomas. (15)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
07/15/2024	Document updated with literature review. Coverage unchanged. No references added; one updated.

03/15/2023	Reviewed. No changes.
05/15/2022	Document updated with literature review. Coverage unchanged. Updated reference 15.
06/15/2021	Reviewed. No changes.
04/15/2020	Document updated with literature review. Coverage unchanged. The following references were added/updated: 14-15. Title changed from: Hematopoietic Stem-Cell Transplantation for Malignant Astrocytomas and Gliomas.
06/18/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. Coverage unchanged.
06/01/2016	Reviewed. No changes.
01/15/2015	Document updated with literature review. Coverage language modified, without change to coverage position. CPT/HCPCS code(s) updated. Title changed from: Stem-Cell Transplant for Malignant Astrocytomas and Gliomas.
10/15/2013	Document updated with literature review. The following was added: 1) Donor leukocyte infusion and hematopoietic progenitor cell boost are considered experimental, investigational and unproven; and 2) Any related services for the treatment of malignant astrocytomas and gliomas, such as short tandem repeat (STR) markers, are considered experimental, investigational and unproven. Otherwise, coverage unchanged. Description and Rationale significantly revised. Document title changed from Stem-Cell Transplant for Astrocytomas and Gliomas.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem Cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies. Stem cell transplant remains experimental, investigational and unproved when used to treat astrocytomas and gliomas. NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem Cells; • Donor Leukocyte Infusion (DLI); and Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies.