MEDICAL POLICY

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION IN THE TREATMENT OF GERM-CELL TUMORS
POLICY NUMBER	MP 9.052

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**5/1/2025**

I. POLICY

Single autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** as salvage therapy for germ-cell tumors:

- in individuals with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; **or**
- in individuals with unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease. (See Policy Guidelines for prognostic factors.)

Tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered **medically necessary** for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

Autologous HCT is considered **investigational** as a component of first-line treatment for germ-cell tumors. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Allogeneic HCT is considered **investigational** to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous HCT. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

The favorable and unfavorable prognostic factors listed below are derived from the current National Comprehensive Cancer Network guidelines and DeVita et al's textbook *Cancer: Principles and Practice of Oncology* (2015, pp. 988-1004).

Individuals with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response to initial chemotherapy, low levels of serum markers, and low volume disease.

Individuals with unfavorable prognostic factors are those with an extra testicular primary site, an incomplete response to initial therapy, high levels of serum markers, high-volume disease, or relapsing mediastinal nonseminomatous germ cell tumors.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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GERM CELL TUMORS

Germ cell tumors are composed primarily of testicular neoplasms as well as ovarian and extragonadal germ cell tumors (no primary tumor in either testis or ovary). Germ cell tumors are classified by their histology, stage, prognosis, and response to chemotherapy.

The most common testicular germ cell tumors are seminomas; all other histologic types are collectively referred to as nonseminomatous tumors. Nonseminomatous tumor types include embryonal cell tumor, yolk sac tumor, and teratomas. Malignant germ cell tumors of ovarian origin are classified as dysgerminomas or nondysgerminomas. Similarly, nondysgerminomas include immature teratomas, embryonal cell tumors, yolk sac tumor, polyembryoma, and mixed germ cell tumors.

Staging

Stage depends on location and extent of the tumor, using the American Joint Committee on Cancer's TNM system. TNM stages, modified by serum concentrations of markers for tumor burden (S0-3) when available, are grouped by similar prognoses. Markers used for germ cell tumors include human β-chorionic gonadotropin, lactate dehydrogenase, and α-fetoprotein. However, most patients with pure seminoma have normal α-fetoprotein concentrations. For testicular tumors, stages IA to B tumors are limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); stages IIA to C have increasing size and number of tumor-involved lymph nodes, and at least 1 marker moderately elevated above the normal range (S1); and stages IIIA to C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

Germ cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, extent of primary tumor, and serum marker levels. Good-risk pure seminomas can be at any primary site but are without nonpulmonary visceral metastases or marker elevations. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated human chorionic gonadotropin and/or lactate dehydrogenase. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated α-fetoprotein (due to mixture with nonseminomatous components) are managed as nonseminomatous germ cell tumors. Good- and intermediate-risk nonseminomatous germ cell tumors have testicular or retroperitoneal tumors without nonpulmonary visceral metastases, and either S1 (good-risk) or S2 (intermediate) levels of marker elevations. Poor-risk tumors have mediastinal primary tumors, or nonpulmonary visceral metastases, or the highest level (S3) of marker elevations.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood is discussed in MP-9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize

graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

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.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have previously untreated germ cell tumors who receive autologous HCT as first-line therapy, the evidence includes randomized controlled trials (RCTs). Results from RCTs have shown that autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (e.g., standard-dose chemotherapy). Study sample sizes were relatively small and might have been underpowered to detect

differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes an RCT and several case series. The single published RCT did not find improved outcomes with high-dose chemotherapy (HDC) and autologous HCT compared with standard-dose HCT. Progression-free and OS rates varied by prior treatment experience, prognostic factors, number of high-dose chemotherapy and autologous stem cell transplantation cycles, and whether additional consolidation treatment such as radiation therapy was included. However, 2- and 3-year progression-free survival rates of 50% to 60% have consistently been achieved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have germ cell tumors who receive tandem autologous transplantation and sequential HDC, the evidence includes an RCT, several retrospective cohort studies, and a comparative effectiveness review. The RCT reported a higher rate of treatment-related mortality with sequential HDC compared with single HDC. However, 5 -year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (i.e., first vs. subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk-stratify patients. Tandem autologous transplant or transplant with sequential HDC has not shown a benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. There were no RCTs or nonrandomized comparative studies evaluating allogeneic HCT for germ cell tumors. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies, 3 academic medical centers, and 5 Blue Distinction Centers for Transplants while this policy was under review in 2010. There was general agreement with the policy statements regarding the use of single autologous hematopoietic cell transplantation (HCT) as salvage therapy, the use of autologous HCT as first-line treatment, and the use of allogeneic HCT. Seven reviewers felt that tandem or sequential HCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; 2 reviewers felt that tandem or sequential HCT was investigational.

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V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Allogeneic hematopoietic cell transplantation is investigational for treatment germ-cell tumors; therefore, not covered:

Procedure Codes							
38205	38230	38240	38242				

Covered when medically necessary:

Procedure Codes							
38204	38206	38207	38208	38209	38210	38211	38212

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38213	38214	38215	38232	38241	S2150		

ICD-10-CM Diagnosis Codes	Description
C38.1	Malignant neoplasm of anterior mediastinum
C38.2	Malignant neoplasm of posterior mediastinum
C38.3	Malignant neoplasm of mediastinum, part unspecified
C48.0	Malignant neoplasm of retroperitoneum
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
C56.9	Malignant neoplasm of unspecified ovary
C62.00	Malignant neoplasm of unspecified undescended testis
C62.01	Malignant neoplasm of undescended right testis
C62.02	Malignant neoplasm of undescended left testis
C62.10	Malignant neoplasm of unspecified descended testis
C62.11	Malignant neoplasm of descended right testis
C62.12	Malignant neoplasm of descended left testis
C62.90	Malignant neoplasm of unspecified testis, unspecified whether descended or undescended
C62.91	Malignant neoplasm of right testis, unspecified whether descended or undescended
C62.92	Malignant neoplasm of left testis, unspecified whether descended or undescended
C75.3	Malignant neoplasm of pineal gland

IX. REFERENCES

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X. POLICY HISTORY

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MP 9.052	**02/27/2020 Consensus Review**. References updated, no change to coding or policy statements.

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	02/09/2021 Consensus Review. Policy statement unchanged. Reference, background, and rationale updated. Coding reviewed.
	09/07/2021 Administrative Update. New code C56.3 added. Effective 10/01/2021
	02/16/2022 Consensus Review. No change to policy statement. References updated. Coding reviewed. NCCN statement added.
	03/13/2023 Consensus Review. No changes to policy statement. References updated. Coding reviewed.
	03/11/2024 Consensus Review. No changes to policy statement. References updated. Coding reviewed with no coding changes. Title change to add the word “extracranial” for better description.
	01/22/2025 Consensus Review. Title change to remove extracranial. Removed NCCN statement. References updated. Coding reviewed and no changes.

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