Policy Number	**SUR703.045**
Policy Effective Date	**08/01/2025**

Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
SUR703.002: Hematopoietic Cell Transplantation (HCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information)

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.**

Coverage

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 individuals with platinum-refractory disease. (See Policy Guidelines section 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 experimental, investigational and/or unproven** as a component of first-line treatment for germ cell tumors.

Allogeneic HCT **is considered experimental, investigational and/or unproven** to treat germ cell tumors, including, but not limited to, its use as therapy after a prior failed autologous HCT.

Policy Guidelines

The favorable and unfavorable prognostic factors listed below are derived from the current National Comprehensive Cancer Network guidelines and DeVita et al. (27)

- 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.

Description

Therapy for germ cell tumors is generally dictated by several factors, including disease stage, tumor histology, primary site of tumor, and response to chemotherapy. Patients with unfavorable prognostic factors may be candidates for hematopoietic cell transplantation (HCT).

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. (1) 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. (2) 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 (T describes the size of the original [primary] tumor and whether it has invaded nearby tissue; N describes nearby [regional] lymph nodes that are involved; and M describes distant metastasis [spread of cancer from one part of the body to another]). TNM stages, modified by serum concentrations of markers for tumor burden (S0 to 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 one 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 to 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 the 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 from 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.

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. Human leukocyte antigens 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.

<u>Conditioning for Hematopoietic Cell Transplantation</u>

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. Reduced-intensity conditioning 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 policy, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative.

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, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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.

Autologous Hematopoietic Cell Transplantation as First-Line Therapy for Germ Cell Tumors

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic cell transplantation (HCT) in individuals who have previously untreated germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with previously untreated germ cell tumors.

Interventions

The therapy being considered is autologous HCT.

Comparators

The following practices are currently being used to make decisions about the treatment of previously untreated germ cell tumors: standard-dose chemotherapy. Therapy for germ cell tumors is generally dictated by stage, risk subgroup, and tumor histology. Testicular cancer is divided into seminomatous and nonseminomatous types for treatment planning because seminomas are more sensitive to radiotherapy. Stage I testicular seminomas may be treated by orchiectomy with or without radiation or single-dose carboplatin adjuvant therapy. Nonseminomatous stage I testicular tumors may be treated with orchiectomy with or without retroperitoneal lymph node dissection. Higher stage disease typically involves treatment that incorporates chemotherapy. First-line chemotherapy for good- and intermediate-risk individuals with higher stage disease is usually three or four cycles of a regimen combining cisplatin and etoposide, with or without bleomycin depending on histology and risk group. Chemotherapy is often followed by surgery to remove residual masses. Second-line therapy often consists of combined therapy with ifosfamide/mesna and cisplatin, plus vinblastine, paclitaxel, or etoposide (if not used for first-line treatment). Individuals whose tumors are resistant to cisplatin may receive carboplatin-containing regimens. The probability of long-term continuous complete remission diminishes with each successive relapse.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), change in disease status, treatment-related mortality (TRM).

Individuals with previously untreated germ cell tumors have been considered for HCT 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.

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.

Randomized Clinical Trials
Daugaard et al. (2011) reported on the outcomes of a randomized phase 3 study comparing standard-dose cisplatin, etoposide, and bleomycin (BEP) with sequential high-dose cisplatin, etoposide, and ifosfamide plus stem cell support in previously untreated males with poor-prognosis germ cell cancer. (3) The trial aimed to recruit 222 patients but closed with 137 patients from 27 European oncology centers due to slow accrual. Patients were ages 15 to 50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ cell tumor of testicular or extragonadal origin. Median follow-up was 4.4 years; 66 patients in the BEP group and 65 patients in the transplant group were included in the analysis. Toxicity was more severe in patients who received high-dose chemotherapy (HDC), and toxicity-related deaths were reported for two patients who received HDC and in one patient in the BEP arm. There was no improvement in complete response (CR) rate in the HDC arm (44.6%) versus the standard-dose arm (33.3%; p=0.18). There was no difference in failure-free survival between the two groups. At 2 years, failure-free survival rates were 44.8% (95% confidence interval [CI], 32.5% to 56.4%) and 58.2% (95% CI, 48.0% to 71.9%), respectively, for the standard- and high-dose arms. The difference was not statistically significant (p=0.06). The OS did not differ between groups (p>0.1). The authors concluded that HDC given as part of first-line therapy does not improve outcomes in patients with poor-prognosis germ cell tumors.

Motzer et al. (2007) reported on a phase 3 prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ cell tumors. (4) Median patient age was 28 years. Patients were randomized to conventional chemotherapy (4 cycles of BEP; n=111) or 2 cycles of BEP followed by 2 cycles of HDC with autologous HCT. Median follow-up was 51 months. The 1-year durable CR rate was 52% after BEP plus HDC with HCT, and 48% after BEP

alone (p=0.53). There was no survival difference at 106 months for patients treated with HDC and HCT (68%) compared with patients treated with conventional chemotherapy (69%).

Droz et al. (2007) assessed the impact of HDC plus HCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ cell tumors. (5) Patients were randomized to 4 cycles every 21 days of vinblastine, etoposide, cisplatin, and bleomycin (n=57) or a slightly modified regimen followed by HDC plus autologous HCT (n=57). In an intention-to-treat analysis, the CR rates were 56% and 42% for the conventional and HDC groups, respectively (p=0.099). Median follow-up was 9.7 years, and no significant difference in OS was found between groups (p=0.167).

Section Summary: Autologous Hematopoietic Cell Transplantation as First Line Therapy for Germ Cell Tumors

For individuals who have previously untreated germ cell tumors who receive autologous HCT as first-line therapy, the evidence includes RCTs. Results from the 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.

Autologous Hematopoietic Cell Transplant for Relapsed or Refractory Germ Cell Tumors

Clinical Context and Therapy Purpose

The purpose of autologous HCT in individuals who have relapsed or refractory germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with relapsed or refractory germ cell tumors.

Interventions

The therapy being considered is autologous HCT.

Comparators

The following practices are currently being used to make decisions about the treatment of previously untreated germ cell tumors: standard-dose chemotherapy. Therapy for germ cell tumors is generally dictated by stage, risk subgroup, and tumor histology. Testicular cancer is divided into seminomatous and nonseminomatous types for treatment planning because seminomas are more sensitive to radiotherapy. Stage I testicular seminomas may be treated by orchiectomy with or without radiation or single-dose carboplatin adjuvant therapy. Nonseminomatous stage I testicular tumors may be treated with orchiectomy with or without retroperitoneal lymph node dissection. Higher stage disease typically involves treatment that incorporates chemotherapy. First-line chemotherapy for good- and intermediate-risk

individuals with higher stage disease is usually three or four cycles of a regimen combining cisplatin and etoposide, with or without bleomycin depending on histology and risk group. Chemotherapy is often followed by surgery to remove residual masses. Second-line therapy often consists of combined therapy with ifosfamide/mesna and cisplatin, plus vinblastine, paclitaxel, or etoposide (if not used for first-line treatment). Individuals whose tumors are resistant to cisplatin may receive carboplatin-containing regimens. The probability of long-term continuous complete remission diminishes with each successive relapse.

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

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.

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.

Randomized Controlled Trials
Pico et al. (2005) reported on a randomized trial comparing 4 cycles of conventional-dose chemotherapy with 3 cycles of the same regimen followed by carboplatin-based HDC plus autologous HCT in 280 patients who had relapsed after a complete or partial remission following first-line therapy with a cisplatin-based regimen. (6) The authors reported no significant differences between treatment arms in 3-year event-free survival (EFS) or OS. However, the trial began before international consensus (7) had established the current risk group definitions; thus, Pico et al. (2005) likely included patients now considered to have good prognosis at relapse. Furthermore, while 77% and 86% of patients in the control and experimental arms, respectively, had at least 1 elevated serum tumor marker, they did not report how highly elevated rates were or compare arms with respect to the marker thresholds that presently determine risk level (S1 to 3). Finally, HDC in the experimental arm followed 3 cycles of conventional-dose chemotherapy, which differs from most current practice in the United States, in which a single cycle is used before HDC. As a consequence, 38 (28%) of 135 patients randomized to the HDC arm did not receive HDC because of progression, toxicity, or withdrawal of consent.

Case Series
Zschäbitz et al. (2018) reported a retrospective analysis of the experience of two referral centers using HDC and autologous stem cell transplantation (ASCT) for relapsed or refractory

germ cell tumors. (8) Forty-six patients treated with HDC/ASCT between 2000 and 2016 were identified; 52% of whom were categorized as poor-risk by the International Prognostic Factors Study Group prognosis score. HDC/ASCT was performed as the first salvage regimen in 67% of patients. Further consolidation therapy after HDC/ASCT was performed with 41% of patients undergoing resection of the residual tumor. In patients who were in complete remission after HDC/ASCT and in those who received residual tumor resection or radiotherapy as consolidation median progression-free survival was 17.7 months (range 2 to 185 months) and median OS had not been reached with 64% of patients being alive at a median follow-up time of 41 months. Median progression-free survival (PFS) and OS in patients who did not achieve a CR was 3.3 months (95% CI, 1.0-5.5 months) and 6.4 months (95% CI, 5.6-7.2 months) in those who had no further consolidation treatment.

Adra et al. (2017) reported a retrospective analysis of a single-institution experience of using HDC/ASCT for relapsed or refractory germ cell tumors. (9) Between 2004 and 2014, there were 364 consecutive patients with germ cell tumors who progressed after cisplatin-based combination chemotherapy; 341 received two consecutive courses of HDC consisting of 700 mg/m^2 carboplatin and 750 mg/m^2 etoposide, each for 3 consecutive days, and each followed by peripheral blood stem cell transplant. At a median follow-up of 3.3 years, patients with pure seminoma had the highest cure rate, with a 2-year PFS of 90% (95% CI, 81% to 95%). Remissions were achieved in poor-prognosis patients who received HDC as third-line or subsequent therapy (2-year PFS, 49%) and in patients with platinum-refractory disease (2-year PFS, 33%). Adverse events were notable with nine treatment-related deaths due to infectious complications, hepatic failure, and secondary leukemia.

Nieto et al. (2015) reported on 43 male patients with poor-risk relapsed or refractory germ cell tumors who received HDC and autologous HCT. (10) Primary tumors were testicular in 32 patients, mediastinal in 7 patients, and retroperitoneal in 4 patients. Median follow-up was 46 months (range, 9 to 84 months). At follow-up, the relapse-free survival rate was 55.8% and the OS rate was 58.1%. Relapse-free survival rates were 66% in patients with testicular primaries, 28.5% in patients with mediastinal primaries, and 25% in patients with retroperitoneal primaries.

Baek et al. (2013) reported on results of a small feasibility study of HDC followed by HCT for patients with relapsed or progressed central nervous system (CNS) germ cell tumors. (11) Investigators enrolled 11 patients with nongerminomatous (i.e., nonseminomatous) germ cell tumors and 9 patients with germinomatous stem cell tumors, all of whom had received conventional chemotherapy with or without radiotherapy before HCT. Sixteen patients received an initial course of HDC with carboplatin, thiopental, and etoposide followed by HCT, and 9 of them received a second course of HDC with cyclophosphamide-melphalan followed by a second HCT (see the tandem and sequential HCT for germ cell tumors section next). Twelve patients remained alive at a median follow-up of 47 months (range, 22 to 90 months), with a 3-year OS probability estimate of 59.1%.

Seftel et al. (2011) conducted a multicenter study of consecutive patients undergoing a single autologous HCT for germ cell tumor between 1986 and 2004. (12) For 71 subjects, median follow-up was 10.1 years. Median age was 31 years (range, 16 to 58 years). Sixty-seven patients had nonseminomatous germ cell tumors and 4 had seminomatous germ cell tumors. Fifty-seven patients had primary gonadal disease and 14 had primary extragonadal disease. Of the latter, 11 patients presented with primary mediastinal disease, 2 presented with primary CNS disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HCT for relapsed disease after achieving an initial CR. Of these, 24 patients underwent autologous HCT after a first relapse and 4 underwent transplant after a second relapse. An additional 36 patients achieved only an incomplete response after initial therapy and proceeded to autologous HCT after salvage chemotherapy for active residual disease. The OS rate at 5 years was 44.7% (95% CI, 32% to 56.5%) and the EFS rate was 43.5% (95% CI, 31.4% to 55.1%). There were 7 (10%) treatment-related deaths within 100 days of transplant. Three (4.2%) patients developed secondary malignancies. Of 33 relapses, 31 occurred within 2 years of the transplant. Two very late relapses occurred 13 and 11 years after transplant. In a multivariate analysis, a favorable outcome was associated with International Germ Cell Consensus Classification good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Section Summary: Autologous Hematopoietic Cell Transplantation for Relapsed or Refractory Germ Cell Tumors

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 HDC and autologous HCT compared with standard-dose HCT. Case series had a wide range of sample sizes. Progression-free and OS rates varied by prior treatment experience, prognostic factors, number of HDC and ASCT cycles and whether additional consolidation treatment such as radiation therapy was included. However, 2- and 3-year progression-free survival rates of 50-60% have consistently been achieved.

Tandem Autologous Hematopoietic Cell Transplant and Sequential High Dose Chemotherapy for Germ Cell Tumors

Clinical Context and Therapy Purpose

The purpose of tandem autologous HCT in individuals who have germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with germ cell tumors.

Interventions

The therapy being considered is tandem autologous HCT, including the use of sequential HDC.

Comparators

The following practices are currently being used to make decisions about treatment of previously untreated germ cell tumors: standard-dose chemotherapy and single autologous HCT.

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

If a transplant were to be performed, the follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

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.

Randomized Controlled Trials
Lorch et al. (2007) compared a single HDC with sequential HDC plus autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ cell tumors. (13) Patients were randomized to 2 different HDC regimens (arm A, arm B). Most tumors were gonadal primaries; 10% of patients in arm A had retroperitoneal, mediastinal, or CNS primaries, and 11% of patients in arm B had retroperitoneal or mediastinal primaries. This represented the first salvage therapy received for 86% of the patients in arm A and 85% in arm B, whereas 14% in arm A and 15% in arm B had received one or more previous salvage regimens before randomization. A total of 111 (51%) of 216 patients were randomized to sequential high-dose therapy, and 105 (47%) of 216 patients were randomized to single high-dose therapy. The trial was stopped prematurely after recruitment of 216 patients as a result of excess treatment-related mortality in arm B (sequential). There was a planned interim analysis after the inclusion of 50% of the required total number of patients. Survival analyses were performed on an intention-to-treat basis.

At a median follow-up of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression-free. At 1 year, EFS, PFS, and OS rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B ($p>0.05$ for all comparisons). Survival rates were not reported separately by primary tumor site. No difference in survival probabilities was found between the single and sequential high-dose regimens; however, sequential high-dose therapy was better tolerated and resulted in fewer treatment-related deaths. Treatment-related deaths, mainly from sepsis and cardiac toxicity, were less frequent in arm A (4/108 [4%] patients) than in arm B (16/103 [16%] patients; $p<0.01$). The authors attributed the higher rate of treatment-related deaths in arm B to the higher dosages

per HCT cycle in the arm B regimen compared with arm A, as well as the toxic renal and cardiac effects of cyclophosphamide used in arm B.

Lorch et al. (2012) reported long-term results from this trial; 5-year PFS rates were 47% (95% CI, 37% to 56%) in arm A and 45% (95% CI, 35% to 55%) in arm B (hazard ratio [HR], 1.16; 95% CI, 0.79 to 1.70; p=0.454). (14) Five-year OS rates were 49% (95% CI, 40% to 59%) in arm A and 39% (95% CI, 30% to 49%) in arm B (HR, 1.42; 95% CI, 0.99 to 2.05; p=0.057). The authors concluded that patients with relapsed or refractory germ cell tumors could achieve durable long-term survival after single as well as tandem HCT plus sequential HDC and that fewer early deaths related to toxicity translated into superior long-term OS after HCT plus sequential HDC.

Nonrandomized Clinical Trials

Lotz et al. (2005) reported on the results of a phase 2 study on 3 consecutive cycles of HDC regimens supported by autologous HCT in 45 poor-prognosis patients with relapsed germ cell tumors. (15) From 1998 to 2001 (median follow-up, 31.8 months), 45 patients (median age, 28 years) were enrolled. Most patients (76%) had testicular primaries; 13% had mediastinal primaries; 11% had retroperitoneal, hepatic, or unknown primaries. Of all patients, 22 received the complete course. Twenty-five patients died from disease progression and 5 from treatment toxicity. The overall response rate was 37.7%, including an 8.9% CR rate. Median OS was 11.8 months. The 3-year OS and PFS rates were both 23.5%. Authors used the Beyer prognostic score to predict the outcome of HDC and concluded that patients with a Beyer score greater than two did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant or refractory primary mediastinal germ cell tumors do not benefit from HDC.

Observational Studies

Secondino et al. (2024) conducted a retrospective analysis using the European Society for Blood and Marrow Transplantation (EBMT) database to assess HDC with autologous stem cell transplantation (ASCT) in adult patients with primary mediastinal non-seminomatous germ cell tumors. (16) Sixty-nine patients treated between 2000 and 2018 were identified, all classified as poor-risk according to the International Germ Cell Cancer Collaborative Group. HDC was administered as upfront therapy in 34.8%, as first-line salvage therapy in 33.3%, and as later-line treatment in 31.9% of cases. Overall survival rates were 43.3% at 2 years and 34.7% at 5 and 10 years. Progression-free survival was 41.3% at 2 years and 35.8% at 5 and 10 years. Patients treated with HDC as upfront therapy had better 5-year PFS and OS (51.8% and 51.3%, respectively) compared to those treated at relapse (26.8% and 25.9%, respectively). Transplant-related mortality occurred in 4.3% of cases. The authors highlight the need for further research to optimize treatment timing and patient selection in this high-risk population.

Agrawal et al. (2021) reported retrospectively on a series of 445 patients, treated between 2004 and 2017, for metastatic germ cell tumors that had progressed (relapsed) after receiving cisplatin-etopside-based combination chemotherapy and tandem HCT. (17) Patients were excluded from the study if they had late relapse germ cell tumors, defined as ≥2 years after previous therapy. Patients received 2 consecutive courses of HDC (carboplatin and etoposide)

followed by HCT. The primary outcome was 2-year PFS in patients <40 years old (n=329) and in patients ≥40 years old (n=116). The 2-year PFS in patients <40 years old was 58.7% versus 59.6% in patients ≥40 years old (p=.76). The OS for patients <40 years old was 63.9% versus 61.5% in patients ≥40 years old (p=.93). It was concluded that patient age was not an independent predictor of treatment outcomes.

Lazarus et al. (2007) reported on the results of autologous HCT for relapsed testicular/germ cell cancer using registry data from the Center for International Blood and Marrow Transplant Research. (18) Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in 8 countries who received a single or a tandem autologous HCT between 1989 and 2001. Of the 300 patients, 102 received tandem and 198 received single planned autologous HCT. Progression-free survival and OS rates at 1, 3, and 5 years were similar for both groups. The probability of PFS at 5 years for the tandem transplant group was 34% (95% CI, 25% to 44%) versus 38% (95% CI, 31% to 45%) for the single transplant group (p=0.50). The probability of 5-year OS was 35% (95% CI, 25% to 46%) versus 42% (95% CI, 35% to 49%), respectively (p=0.29).

Einhorn et al. (2007) reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with 2 consecutive cycles of HDC for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy. (19) Patients with primary mediastinal nonseminomatous germ cell tumors or tumors with late relapse (≥2 years after previous therapy) were excluded. The patient population included those with initial International Germ Cell Consensus Classification stage defined as low-risk (39%), intermediate-risk (21%), and high-risk (41%) and both platinum-sensitive and refractory disease at the beginning of HDC. Patients received 2 consecutive courses of HDC (carboplatin and etoposide) followed by HCT. Results from this experienced center showed that, of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy (i.e., first salvage setting), 94 (70%) were disease-free during follow-up; 22 (45%) of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer refractory to standard-dose platinum, 18 (45%) were disease-free. Caveats to the Einhorn et al. (2007) study included the lack of a validation set for the prognostic scoring system used, the unanswered question of the role of high-dose versus conventional-dose chemotherapy in the first salvage setting, and the lack of a universally accepted prognostic scoring system in this setting.

In a subsequent study from the same center as the Einhorn et al. (2007) study, Suleiman et al. (2013) evaluated outcomes for 12 patients with recurrent primary mediastinal nonseminomatous germ cell tumors after initial treatment with cisplatin-containing combination chemotherapy, a population excluded from their previous study, who were treated with tandem HCT. (20) Patients received 2 consecutive courses of HDC (carboplatin and etoposide) followed by HCT. Overall outcomes were poor, with a median survival of 11 months (range, 4 to 52 months), but 3 of 12 patients achieved a CR. One patient remained disease-free at 50 months of follow-up, and one remained disease-free after tandem HCT and subsequent mediastinal surgery at 52 months of follow-up.

Pal et al. (2013) reported on 5-year follow-up results for 48 patients with relapsed germ cell tumors enrolled in a retrospective case series to evaluate the effectiveness of 2 sequential cycles of chemotherapy with paclitaxel, etoposide, and carboplatin in the first cycle, high-dose paclitaxel, ifosfamide, and carboplatin in the second, followed by HCT. (21) Forty-three (91.5%) patients had nonseminomatous histology. Most patients (n=39) had received 2 prior chemotherapy regimens; 6 patients had received 3 prior regimens. Thirty-four patients had intermediate-risk classification by the Beyer score and the remainder had a high-risk classification. Of the 48 patients enrolled, 17 received only 1 course of paclitaxel, etoposide, and carboplatin, 11 due to progressive disease, 5 due to toxicities, and 1 due to a severe fungal infection. Seventeen of the 48 patients enrolled were alive and progression-free at a median of 123.2 months (range, 51.6 to 170.2 months); 25 died, most (n=23) due to disease progression. Of the 23 patients alive after receiving per-protocol therapy, 18 were contacted for interviews at a median 115.6 months (range, 38.9 to 185.9 months) post-enrollment and underwent a cancer-related quality-of-life assessment with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). The overall average score on the questionnaire was 87.04; the authors compared quality-of-life scores in this cohort with a separate cohort of 150 patients who had germ cell tumors who received chemotherapy; authors reported that patients in their cohort had significantly higher global health scores (87.04 versus 75.62, p=0.02), but lower physical functioning scores (68.9 versus 92.7, p<0.001). The authors concluded that tandem HDC followed by HCT would be a reasonable treatment option for relapsed germ cell tumors, with long-term survivors demonstrating a reasonable quality of life.

A 2012 comparative effectiveness review, conducted for the Agency for Healthcare Research and Quality (AHRQ), on the use of HCT in the pediatric population concluded that, for germ cell tumors, the body of evidence on OS with tandem HCT compared with single HCT was insufficient to draw conclusions. (22)

Section Summary: Tandem Autologous Hematopoietic Cell Transplantation and Sequential High Dose Chemotherapy for Germ Cell Tumors

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 than with single HDC. However, five-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 versus 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.

Allogeneic Hematopoietic Cell Transplant for Germ Cell Tumors

Clinical Context and Therapy Purpose

The purpose of allogeneic HCT in individuals who have germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with germ cell tumors.

Interventions
The therapy being considered is allogeneic HCT.

Comparators
The following practices are currently being used to make decisions about treatment of previously untreated germ cell tumors: standard-dose chemotherapy and autologous HCT.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, and treatment-related mortality.

If a transplant were to be performed, the follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

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.

No RCTs or nonrandomized comparative studies evaluating allogeneic HCT for germ cell tumors were identified. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT. (23)

Section Summary: Allogeneic Hematopoietic Cell Transplant for Germ Cell Tumors
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.

Summary of Evidence

For individuals who have previously untreated germ cell tumors who receive autologous hematopoietic cell transplantation (HCT) as first-line therapy, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) and morbidity. 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 that the technology results in an improvement in the net health outcome.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes an RCT and several case series. Relevant outcomes are OS, DSS, and TRM and morbidity. The single published RCT did not find improved outcomes with high dose chemotherapy (HDC) and autologous HCT compared with standard-dose chemotherapy. Case series had a wide range of sample sizes. 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 50-60% 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. Relevant outcomes are OS, DSS, and TRM and morbidity. The RCT reported a higher rate of TRM 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 versus 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. Relevant outcomes are OS, DSS, and TRM and morbidity. 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 Received through Physician Specialty Societies and Academic Medical Centers
In 2010, clinical input found general agreement with the policy statements regarding the use of single autologous HCT as salvage therapy, the use of autologous HCT as first-line treatment, and the use of allogeneic HCT. Seven of the reviewers felt that tandem autologous transplant or

transplant with sequential HCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; two reviewers felt that tandem transplant or sequential HDC was investigational.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines on ovarian cancer (v1.2025) state that high-dose chemotherapy with stem cell support is among preferred regimens as potentially curative therapy for recurrent malignant germ cell tumors. (24)

Current NCCN guidelines on testicular cancer (v.1.2025) state that second-line chemotherapy regimens for metastatic germ cell tumors include high-dose chemotherapy with stem cell support. (25)

American Society for Transplantation and Cellular Therapy

In 2020, guidelines by the American Society for Transplantation and Cellular Therapy were published on indications for autologous and allogeneic HCT. (26) Recommendations were intended to describe the current consensus on use of HCT within and outside of the clinical trial setting. Recommendations on germ cell tumors are listed in Table 1.

Table 1. Recommendations on Allogeneic and Autologous HCT

Indications	Allogeneic HCT	Autologous HCT
Pediatric		
Germ cell tumor, relapse	D	C
Germ cell tumor, refractory	D	C
Adult		
Germ cell tumor, relapse	N	S
Germ cell tumor, refractory	N	S

HCT: hematopoietic cell transplantation; C: clinical evidence available, standard of care; D: developmental (i.e., promising); N: not generally recommended; S: standard of care.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02375204	A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) With High-Dose Chemotherapy Using Mobilizing	420	Jun 2031

	Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors		
Unpublished			
NCT00432094	Autologous Peripheral Blood Stem-Cell Transplant for Germ-Cell Tumors	23	Mar 2021

NCT: national clinical trial.

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, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Chovanec M, Cheng L. Advances in diagnosis and treatment of testicular cancer. BMJ. Nov 28 2022; 379:e070499. PMID 36442868
2. Veneris JT, Mahajan P, Frazier AL. Contemporary management of ovarian germ cell tumors and remaining controversies. Gynecol Oncol. Aug 2020; 158(2):467-475. PMID 32507650
3. Daugaard G, Skoneczna I, Aass N, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). Ann Oncol. May 2011; 22(5):1054-1061. PMID 21059637
4. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic

stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol. Jan 20 2007; 25(3):247-256. PMID 17235042
5. Droz JP, Kramar A, Biron P, et al. Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomized trial. Eur Urol. Mar 2007; 51(3):739-746. PMID 17084512
6. Pico JL, Rosti G, Kramar A, et al. A randomized trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumors. Ann Oncol. Jul 2005; 16(7):1152-1159. PMID 15928070
7. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol. Feb 1997; 15(2):594-603. PMID 9053482
8. Zschabitz S, Distler FA, Krieger B, et al. Survival outcomes of patients with germ cell tumors treated with high-dose chemotherapy for refractory or relapsing disease. Oncotarget. Apr 27 2018; 9(32):22537-22545. PMID 29854297
9. Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. J Clin Oncol. Apr 1 2017; 35(10):1096-1102. PMID 27870561
10. Nieto Y, Tu SM, Bassett R, et al. Bevacizumab/high-dose chemotherapy with autologous stem-cell transplant for poor-risk relapsed or refractory germ-cell tumors. Ann Oncol. Dec 2015; 26(12):2507-2508. PMID 26487577
11. Baek HJ, Park HJ, Sung KW, et al. Myeloablative chemotherapy and autologous stem cell transplantation in patients with relapsed or progressed central nervous system germ cell tumors: results of Korean Society of Pediatric Neuro-Oncology (KSPNO) S-053 study. J Neurooncol. Sep 2013; 114(3):329-338. PMID 23824533
12. Seftel MD, Paulson K, Doocey R, et al. Long-term follow-up of patients undergoing auto-SCT for advanced germ cell tumour: a multicentre cohort study. Bone Marrow Transplant. Jun 2011; 46(6):852-857. PMID 21042312
13. Lorch A, Kollmannsberger C, Hartmann JT, et al. Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. J Clin Oncol. Jul 1 2007; 25(19):2778-2784. PMID 17602082
14. Lorch A, Kleinhans A, Kramar A, et al. Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. J Clin Oncol. Mar 10 2012; 30(8):800-805. PMID 22291076
15. Lotz JP, Bui B, Gomez F, et al. Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of the phase II multicentric TAXIF trial. Ann Oncol. Mar 2005; 16(3):411-418. PMID 15659420
16. Secondino S, Badoglio M, Rosti G, et al. High-dose chemotherapy with autologous stem cell transplants in adult primary non-seminoma mediastinal germ-cell tumors. A report from the Cellular Therapy and Immunobiology working party of the EBMT. ESMO Open. Sep 2024; 9(9):103692. PMID 39241498

17. Agrawal V, Abonour R, Abu Zaid M, et al. Survival outcomes and toxicity in patients 40 years old or older with relapsed metastatic germ cell tumors treated with high-dose chemotherapy and peripheral blood stem cell transplantation. Cancer. Oct 15 2021; 127(20):3751-3760. PMID 34260067
18. Lazarus HM, Stiff PJ, Carreras J, et al. Utility of single versus tandem autotransplants for advanced testes/germ cell cancer: A Center for International Blood and Marrow Transplant Research (CIBMTR) analysis. Biol Blood Marrow Transplant. Jul 2007; 13(7):778-779. PMID 17580256
19. Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ cell tumors. N Engl J Med. Jul 26 2007; 357(4):340-348. PMID 17652649
20. Suleiman Y, Siddiqui BK, Brames MJ, et al. Salvage therapy with high-dose chemotherapy and peripheral blood stem cell transplant in patients with primary mediastinal nonseminomatous germ cell tumors. Biol Blood Marrow Transplant. Jan 2013; 19(1):161-163. PMID 22892555
21. Pal SK, Yamzon J, Sun V, et al. Paclitaxel-based high-dose chemotherapy with autologous stem cell rescue for relapsed germ cell tumor: clinical outcome and quality of life in long-term survivors. Clin Genitourin Cancer. Jun 2013; 11(2):121-127. PMID 23062817
22. Ratko TA, Belinson SE, Brown HM, et al. Hematopoietic stem-cell transplantation in the pediatric population (No. 12-EHC018-EF). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2012.
23. Goodwin A, Gurney H, Gottlieb D. Allogeneic bone marrow transplant for refractory mediastinal germ cell tumour: possible evidence of graft-versus-tumour effect. Intern Med J. Feb 2007; 37(2):127-129. PMID 17229257
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 1.2025. Available at: <https://www.nccn.org> (accessed March 6, 2025).
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer. Version 1.2025. Available at: <https://www.nccn.org> (accessed March 6, 2025).
26. Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. Jul 2020; 26(7):1247-1256. PMID 32165328
27. DeVita VT Jr, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Lippincott Williams & Wilkins. 10th edition. 2015; 2015:988-1004.

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**
08/01/2025	Document updated with literature review. Coverage reorganized with movement of some criteria to Policy Guidelines; no change to policy intent. Added references 1, 2, 16, 24 and 27; others updated.
08/15/2024	Reviewed. No changes.
10/15/2023	Document updated with literature review. The following change was made to Coverage: Changed “patients” to “individuals”. Added/updated the following references: 14, 21, and 22.
05/15/2022	Reviewed. No changes.
12/01/2021	Document updated with literature review. Coverage unchanged. Updated reference 20.
08/15/2020	Reviewed. No changes.
06/01/2019	Document updated with literature review. The following change was made to Coverage: Modified “Tandem sequential autologous HSCT [hematopoietic stem-cell transplantation] 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.” to “Tandem autologous HCT [hematopoietic cell transplantation] 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.” Added references 6, 7, and 21. Title changed from “Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors”.
10/01/2018	Document updated with literature review. Revised coverage statement for content clarification on tandem sequential autologous hematopoietic stem-cell transplantation for testicular tumors; intent of coverage statement remains unchanged. Information on unfavorable prognostic factors added to NOTE 2. References 9 and 20 added; one reference removed.
06/01/2017	Reviewed. No changes.
07/15/2016	Document updated with literature review. Coverage unchanged.
02/01/2015	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 Germ-Cell Tumors (GCTs).
10/15/2013	Document updated with literature review. The following was added: 1) AutoSCS may be considered medically necessary for treatment of germ-cell tumors (GCTs) in patients with a) favorable prognostic factors that have

	failed a previous course of conventional-dose salvage chemotherapy; or b) unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy); 2) tandem or sequential AutoSCS for testicular tumors may be considered medically necessary; and 3) any other sequence or combination of tandem AutoSCS and AlloSCS, or triple SCS are considered experimental, investigational and unproven; 4) hematopoietic progenitor cell boost is considered experimental, investigational and unproven; and 5) Any related services, other than AutoSCS and/or tandem or sequential AutoSCS for testicular tumors determined to be medically necessary, for the treatment of GCT's, such as short tandem repeat (STR) markers, are considered experimental, investigational and unproven.
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 continues to be medically necessary when stated criteria are met. 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.