

**8.01.35 Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors**

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Section: 11.0 Transplant Page: Page 1 of 21

**Policy Statement**

Single autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** as salvage therapy for germ cell tumors in **any** of the following:

- I. In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy
- II. In patients with unfavorable prognostic factors in **either** of the following:
  - A. As initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy)
  - B. In patients 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 **investigational** as a component of first-line treatment for germ cell tumors.

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.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

**Policy Guidelines**

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

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

Patients 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. Patients 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.

**Coding**

In 2003, CPT centralized codes describing allogeneic and autologous hematopoietic stem cell support services to the hematology section (CPT 38204-38242). Not all codes are applicable for each high-dose chemotherapy stem cell support procedure. For example, Plans should determine if cryopreservation is performed. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38207-38215).

The following CPT code describes cryopreservation and storage:

- **38207:** Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

The following CPT codes describe thawing and washing of cryopreserved cells:

- **38208:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
- **38209:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

The following CPT codes describe certain cell types being depleted:

- **38210:** Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
- **38211:** Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
- **38212:** Transplant preparation of hematopoietic progenitor cells; red blood cell removal
- **38213:** Transplant preparation of hematopoietic progenitor cells; platelet depletion
- **38214:** Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion

The following CPT code describes plasma cell concentration:

- **38215:** Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer

## 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).

## Related Policies

- N/A

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

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

## Rationale

### Background

#### 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 to 3) when available, are grouped by similar prognoses. Markers used for germ cell tumors include human  $\beta$ -chorionic gonadotropin, lactate dehydrogenase, and  $\alpha$ -fetoprotein. However, most patients with pure seminoma have normal  $\alpha$ -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 to 3).

Germ cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, extent of the 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  $\alpha$ -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 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 transplantation is discussed in detail in Blue Shield of California Medical Policy: Placental and 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 lympho-ablation, 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.

#### **Literature Review**

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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 stem cell transplantation in patients 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 question addressed in this evidence review is: Does autologous stem cell transplantation used as treatment of previously untreated germ cell tumors improve net health outcomes?

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

#### **Populations**

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

#### **Interventions**

The therapy being considered is autologous stem cell transplantation.

#### **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. Non-seminomatous 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 patients with higher stage disease is usually 3 or 4 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). Patients 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.

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

#### **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.

## Review of Evidence

### 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.<sup>1</sup> 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 2 patients who received HDC and in 1 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%;  $p=.18$ ). There was no difference in failure-free survival between the 2 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 ( $p=.06$ ). The OS did not differ between groups ( $p>.1$ ). 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.<sup>2</sup> 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 hematopoietic cell transplantation (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 ( $p=.53$ ). 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.<sup>3</sup> 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 ( $p=.099$ ). Median follow-up was 9.7 years, and no significant difference in OS was found between groups ( $p=.167$ ).

### 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 Stem Cell Transplant for Relapsed or Refractory Germ Cell Tumors Clinical Context and Therapy Purpose

The purpose of autologous stem cell transplantation in patients 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 question addressed in this evidence review is: Does autologous stem cell transplantation used as treatment of relapsed or refractory germ cell tumors improve net health outcomes?

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

### **Populations**

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

### **Interventions**

The therapy being considered is autologous stem cell transplantation.

### **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. Non-seminomatous 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 patients with higher stage disease is usually 3 or 4 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). Patients 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 treatment-related mortality.

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.

### **Review of Evidence**

#### **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.<sup>4</sup> The authors reported no significant differences between treatment arms in 3-year event-free survival or OS. However, the trial began before international consensus<sup>5</sup> had established the current risk group definitions; thus, Pico et al (2005) likely included patients now considered to have a 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 2 referral centers using HDC and autologous stem cell transplantation (ASCT) for relapsed or refractory germ cell tumors.<sup>6</sup> Forty-six patients treated with HDC /ASCT between 2000-2016 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; 95% CI: n.a.) 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 to 5.5 months) and 6.4 months (95% CI: 5.6 to 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.<sup>7</sup> Between 2004 and 2014, there were 364 consecutive patients with germ cell tumors who progressed after cisplatin-based combination chemotherapy; 341 received 2 consecutive courses of HDC consisting of 700 mg/m<sup>2</sup> carboplatin and 750 mg/m<sup>2</sup> 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 9 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.<sup>8</sup> 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.<sup>9</sup> 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 tumors between 1986 and 2004.<sup>10</sup> 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 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 event-free survival 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 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.

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

#### **Clinical Context and Therapy Purpose**

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

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

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

#### **Populations**

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

#### **Interventions**

The therapy being considered is tandem autologous stem cell transplantation 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 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

### Review of Evidence

#### Randomized Controlled Trials

Lorch et al (2007) compared single HDC with sequential HDC plus autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ cell tumors.<sup>11</sup> 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 1 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, event-free survival, PFS, and OS rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B ( $p > .05$  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;  $p < .01$ ). 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;  $p = .454$ ).<sup>12</sup> 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;  $p = .057$ ). 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.<sup>13</sup> 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. 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 2 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

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-etoposide-based combination chemotherapy and tandem HCT.<sup>14</sup> Patients were excluded from the study if they had late relapse germ cell tumors, defined as  $\geq 2$  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  $\geq 40$  years old ( $n=116$ ). The 2-year PFS in patients  $< 40$  years old was 58.7% versus 59.6% in patients  $\geq 40$  years old ( $p=.76$ ). The OS for patients  $< 40$  years old was 63.9% versus 61.5% in patients  $\geq 40$  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.<sup>15</sup> 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. PFS 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 ( $p=.50$ ). The probability of 5-year OS was 35% (95% CI, 25% to 46%) versus 42% (95% CI, 35% to 49%), respectively ( $p=.29$ ).

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.<sup>16</sup> Patients with primary mediastinal nonseminomatous germ cell tumors or tumors with late relapse ( $\geq 2$  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.<sup>17</sup> 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 1 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.<sup>18</sup> 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 were 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,  $p=.02$ ), but lower physical functioning scores (68.9 versus 92.7,  $p<.001$ ). 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, 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.<sup>19</sup>

### **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 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.

### **Allogeneic Hematopoietic Stem Cell Transplant for Germ Cell Tumors Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: Does allogeneic stem cell transplantation used as treatment of germ cell tumors improve net health outcomes?

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

#### **Populations**

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

#### **Interventions**

The therapy being considered is allogeneic stem cell transplantation.

**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.

**Review of Evidence**

No RCTs or nonrandomized comparative studies evaluating allogeneic HCT (allo-HCT) for germ cell tumors were identified. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allo-HCT.<sup>20</sup>

**Section Summary: Allogeneic Hematopoietic Stem Cell Transplant for Germ Cell Tumors**

For individuals who have germ cell tumors who receive allo-HCT, the evidence includes a case report. There were no RCTs or nonrandomized comparative studies evaluating allo-HCT for germ cell tumors. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allo-HCT.

**Summary of Evidence**

For individuals who have previously untreated germ cell tumors who receive autologous HCT as first-line therapy, the evidence includes RCTs. Relevant outcomes are OS, DSS, and treatment-related mortality 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 treatment-related mortality and morbidity. 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 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. Relevant outcomes are OS, DSS, and treatment-related mortality and morbidity. 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. Relevant outcomes are OS, DSS, and treatment-related mortality 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.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### 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 from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies, 3 academic medical centers, and 5 Blue Distinction Centers for Transplants 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 autologous transplant or transplant with sequential HCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; 2 reviewers felt that tandem transplant or sequential high-dose chemotherapy was investigational.

### Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.<sup>23</sup> Key findings and recommendations are summarized in Table 1.

**Table 1. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors**

Content Area	Key Point
1 Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2 Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs
3 Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4 OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5 Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines on testicular cancer (v.1.2022) state that second-line chemotherapy regimens for metastatic germ cell tumors include high-dose chemotherapy with stem cell support.<sup>21</sup>

### 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.<sup>22</sup> Recommendations were intended to describe the current consensus on the use of HCT within and outside of the clinical trial setting. Recommendations on germ cell tumors are listed in Table 2.

**Table 2. Recommendations on Allogeneic and Autologous Hematopoietic Cell Transplantation**

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

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 3.

**Table 3. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT00432094	Autologous Peripheral Blood Stem Cell Transplant for Germ-Cell Tumors	23	Jun 2022
NCT02375204	A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) With High-Dose Chemotherapy Using Mobilizing Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors	420	Jun 2024
NCT00936936	High-dose Chemotherapy for Poor-prognosis Relapsed Germ-cell Tumors	64	Oct 2022

NCT: national clinical trial.

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## Documentation for Clinical Review

### Please provide the following documentation:

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history including comorbidities
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
  - Chest x-ray (CXR)
  - PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
  - EKG
  - Echocardiogram
  - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
  - Bone marrow biopsy
  - Lymph node biopsy (as appropriate)
- Laboratory reports

## Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
	38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
	38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
	38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
	38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
	38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
	38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	HCPCS	86812
86813		HLA typing; A, B, or C, multiple antigens
86816		HLA typing; DR/DQ, single antigen
86817		HLA typing; DR/DQ, multiple antigens
86821		HLA typing; lymphocyte culture, mixed (MLC)
S2140		Cord blood harvesting for transplantation, allogeneic
S2142		Cord blood-derived stem-cell transplantation, allogeneic

Type	Code	Description
	S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and posttransplant care in the global definition

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
07/14/2014	Policy title change from Hematopoietic Stem-Cell Transplantation for Germ-Cell Tumors Policy revision with position change
07/31/2015	Coding update
08/31/2015	Policy revision without position change
03/01/2017	Policy title change from Hematopoietic Stem Cell Transplantation in the Treatment of Germ Cell Tumors Policy revision without position change
01/01/2018	Coding update
04/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
11/01/2019	Policy revision without position change
04/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2021	Annual review. No change to policy statement. Literature review updated. Policy title changed from Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumor to current one.
04/01/2022	Annual review. No change to policy statement. Literature review updated.

### Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions,

but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### **Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p><b>Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors 8.01.35</b></p> <p><b>Policy Statement:</b>                      Single autologous hematopoietic cell transplantation (HCT) may be considered <b>medically necessary</b> as salvage therapy for germ cell tumors in <b>any</b> of the following:</p> <ul style="list-style-type: none"> <li>I. In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy</li> <li>II. In patients with unfavorable prognostic factors in <b>either</b> of the following:                             <ul style="list-style-type: none"> <li>A. As initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy)</li> <li>B. In patients with platinum-refractory disease (See Policy Guidelines section for prognostic factors)</li> </ul> </li> </ul> <p>Tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered <b>medically necessary</b> for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.</p> <p>Autologous HCT is considered <b>investigational</b> as a component of first-line treatment for germ cell tumors.</p> <p>Allogeneic HCT is considered <b>investigational</b> to treat germ cell tumors, including, but not limited, to its use as therapy after a prior failed autologous HCT.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered <b>investigational</b>.</p>	<p><b>Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors 8.01.35</b></p> <p><b>Policy Statement:</b>                      Single autologous hematopoietic cell transplantation (HCT) may be considered <b>medically necessary</b> as salvage therapy for germ cell tumors in <b>any</b> of the following:</p> <ul style="list-style-type: none"> <li>I. In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy</li> <li>II. In patients with unfavorable prognostic factors in <b>either</b> of the following:                             <ul style="list-style-type: none"> <li>A. As initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy)</li> <li>B. In patients with platinum-refractory disease (See Policy Guidelines section for prognostic factors)</li> </ul> </li> </ul> <p>Tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered <b>medically necessary</b> for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.</p> <p>Autologous HCT is considered <b>investigational</b> as a component of first-line treatment for germ cell tumors.</p> <p>Allogeneic HCT is considered <b>investigational</b> to treat germ cell tumors, including, but not limited, to its use as therapy after a prior failed autologous HCT.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered <b>investigational</b>.</p>