**Policy Statement**

Autologous and allogeneic hematopoietic cell transplantation are considered investigational to treat advanced stage epithelial ovarian cancer.

**Policy Guidelines**

Stem cell transplantation to treat germ cell tumors of the ovary is considered separately in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors.

**Description**

The use of hematopoietic cell transplantation (HCT) has been investigated to treat patients with epithelial ovarian cancer. Hematopoietic stem cells are infused to restore bone marrow function after cytotoxic doses of chemotherapeutic agents with or without whole body radiotherapy.

**Related Policies**

- Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors

**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**

**Epithelial Ovarian Cancer**

Several types of malignancies can arise in the ovary; epithelial carcinoma is the most common. Epithelial ovarian cancer is the fifth most common cause of cancer death in women. New cases and deaths from ovarian cancer in the United States for 2017 were estimated at 22,440 and...
14080, respectively. Most ovarian cancer patients present with widespread disease, and the National Cancer Institute Surveillance, Epidemiology and Results Program reported a 46.5% five-year survival for all cases between 2007 and 2013.

**Treatment**

Current management for advanced epithelial ovarian cancer is cytoreductive surgery with chemotherapy. Approximately 75% of patients present with International Federation of Gynecology and Obstetrics stage III to IV ovarian cancer and are treated with paclitaxel plus a platinum analogue, the preferred regimen for the newly diagnosed advanced disease. Use of platinum and taxanes has improved progression-free survival and overall survival in advanced disease to between 16 and 21 months and 32 and 57 months, respectively. However, cancer recurs in most women, and they die of the disease because chemotherapy drug resistance leads to uncontrolled cancer growth.

**Hematopoietic Cell Transplantation**

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. 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.

HCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults is largely experimental.

**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 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 technology, two domains are examined: the relevance, and 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.

**Hematopoietic cell transplantation for epithelial ovarian cancer**

**Clinical Context and Therapy Purpose**

The purpose of autologous or allogeneic stem cell transplantation in patients who have epithelial ovarian cancer 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 or allogeneic stem cell transplantation used as part of the treatment of ovarian cancer improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population(s) of interest are patients with advanced epithelial ovarian cancer who have undergone debulking surgery and first-line chemotherapy.

**Interventions**
The therapy being considered is autologous or allogeneic stem cell transplantation. HCT has been investigated as a therapy to overcome drug resistance. HCT has been tested in various patient groups with ovarian cancer to consolidate remission after induction therapy, to treat relapse after a durable response to platinum-based chemotherapy, to treat tumors that relapse after less than six months, to treat refractory tumors.

**Comparators**
The following practices are currently being used to make decisions about the treatment of advanced epithelial ovarian cancer: guideline-based clinical pathways for debulking surgery and platinum-based chemotherapy.

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

**Timing**
Patients with advanced epithelial advanced ovarian cancer have been considered for stem cell transplantation in the setting of remission after induction therapy or relapse after first-line chemotherapy. 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.

**Setting**
Stem cell transplantation is performed in tertiary inpatient settings with specialized expertise.

**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.

This evidence review was informed by a 1998 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment that reached the following conclusions:

- Data were unavailable from RCTs for any of the patient groups studied. Thus, the Assessment was able to compare outcomes only indirectly, using separate studies of high-dose chemotherapy (HDC) and conventional-dose regimens. Although some results reported after HDC appeared encouraging, indirect comparisons did not permit conclusions.
- In previously untreated patients, reported response rates suggested that HDC increased objective response rates compared with patients given conventional-dose chemotherapy. However, this comparison was flawed by age bias and differences in performance status and other baseline characteristics of patients included in the two
sets of studies. Response duration and survival data were unavailable for comparison. Treatment-related mortality was greater after HDC.

- In previously treated patients, objective response rates after HDC also were reportedly higher than after conventional-dose regimens. Subgroup analyses showed higher response rates among platinum-sensitive, optimally debulked patients. Minimum values of the ranges reported across studies for median response duration and survival after HDC were similar to those reported after conventional-dose chemotherapy. However, the maxima for these ranges suggested improved response duration and OS after HDC. In contrast, data from the Autologous Blood and Marrow Transplant Registry did not show similarly high survival for comparable subgroups. Comparison with conventional-dose chemotherapy was again biased due to differences in age distributions, performance status, and other baseline characteristics of patients included in studies of high-dose or conventional chemotherapies.

The 1998 TEC Assessment did not identify any studies reporting outcomes of allogeneic transplants for patients with ovarian cancer. A 1999 TEC Assessment evaluated the use of HDC with allogeneic stem cell support as salvage therapy after a failed prior course of HDC with autologous stem cell support.7 There were no data on outcomes of this strategy as therapy for epithelial ovarian cancer.

Experience with HCT in epithelial ovarian cancer is primarily derived from registry data and phase 2 trials.8,9,10,11 Many registry patients were treated after relapse and others in nonrandomized trials using HDC as first-line treatment. Case selection and retrospective review make interpretation of registry and nonrandomized data difficult.4 Survival analyses from registry data and clinical trials have suggested a possible benefit in treating ovarian cancer patients with HCT.

**Randomized Controlled Trials**

Mobus et al (2007) reported on a phase 3 trial that included 149 patients with untreated ovarian cancer who were randomized, after debulking surgery, to standard chemotherapy or sequential HDC and peripheral blood stem cell support.4 This was the first randomized trial comparing HDC with standard chemotherapy as first-line treatment of ovarian cancer, and investigators found no statistically significant differences in progression-free survival (PFS) or OS between treatments. The trial was powered such that a sample of 208 patients would be needed to detect an absolute improvement of 15% in PFS with a power of 80% and a 1-sided α of 5%. Median patient age was 50 years (range, 20-65 years) and International Federation of Gynecology and Obstetrics stage was IIB or IIC in 4%, stage III in 78%, and stage IV in 17%. Seventy-six percent of patients in the HDC arm received all scheduled chemotherapy cycles. After a median follow-up of 38 months, PFS was 20.5 months in the standard chemotherapy arm and 29.6 months in the HDC arm (hazard ratio, 0.84; 95% confidence interval, 0.56 to 1.26; p=0.40). Median OS was 62.8 months in the standard chemotherapy arm and 54.4 months in the HDC arm (hazard ratio, 1.17; 95% confidence interval, 0.71 to 1.94; p=0.54).

Papadimitriou et al (2008) reported on an RCT comparing the use of HDC with stem cell support as consolidation therapy in patients with advanced epithelial ovarian cancer (International Federation of Gynecology and Obstetrics stage IIC-IV).5 Patients who achieved first complete remission after conventional chemotherapy were randomized to receive or not, high-dose melphalan and autologous HCT. Eighty patients were enrolled in the trial. Of 37 patients allocated to HDC, 11 (30%) did not receive the treatment either due to refusal or failure of peripheral blood stem cell mobilization. In an intention-to-treat analysis, there were no significant differences between arms in time-to-disease progression (p=0.059) or OS (p=0.38).

**Observational Comparative Studies**

Sabatier et al (2012) retrospectively reviewed 163 patients with advanced or metastatic (International Federation of Gynecology and Obstetrics stage IIIIC or IV) epithelial ovarian cancer who were treated at a single institution in France.12 All patients received cytoreductive...
surgery and combination platinum plus taxane chemotherapy. Investigators compared median 
PFS and OS among 60 patients who received subsequent HDC with autologous HCT support and 
103 patients who did not. HDC regimens varied, but all contained alkylation agents. At a 
median follow-up of 47.5 months, PFS in the high-dose and the standard chemotherapy groups 
was 20.1 months and 18.1 months, respectively (p not reported). OS was 47.3 months and 41.3 
months, respectively (p=0.29). In prespecified subgroup analyses, median PFS was significantly 
longer in women younger than age 50 years who received HDC (81.7 months) than in women 
who received standard chemotherapy (11 months; p=0.02); in women older than 50 years, 
median PFS did not differ statistically between groups (17.9 months vs 18.3 months, respectively; 
p=0.81). Similarly, median OS was significantly longer in women younger than age 50 years who 
received HDC (54.6 months) than in women who received standard chemotherapy (36 months; 
p=0.05), but not in women older than 50 years (49.5 months vs 42 months, respectively; p not 
reported). The authors recommended further study of HDC with autologous HCT support in 
patients younger than 50 years.

Summary of Evidence
For individuals who have advanced-stage epithelial ovarian cancer who receive HCT, the 
evidence includes randomized trials and data from case series and registries. The relevant 
outcomes are OS, disease-specific survival, change in disease status, and treatment-related 
mortality and morbidity. Although some observational studies have reported longer survival in 
subsets of women with advanced epithelial ovarian cancer than in women treated with 
standard chemotherapy, none of the randomized trial evidence has shown a benefit from HCT 
in this population. Overall, the evidence has not shown that HCT improves health outcomes in 
treating epithelial ovarian cancer, including survival, compared with conventional standard 
doses of chemotherapy. The evidence is insufficient to determine the effects of the technology 
on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
Current National Comprehensive Cancer Network guidelines (v.2.2018) do not address 
hematopoietic cell transplantation for epithelial ovarian cancer for patients either with newly 
diagnosed or with relapsed or refractory disease.3

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services currently have the following national 
noncoverage decision on autologous stem cell transplantation [AuSCT]: “Insufficient data exist 
to establish definite conclusions regarding the efficacy of AuSCT for the following condition(s): 
Solid tumors (other than neuroblastoma).”13

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in January 2018 did not identify any ongoing or unpublished trials 
that would likely influence this review.

References

December 5, 2017.

2. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer 

Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal
8.01.23  Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
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7. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem cell support for relapse following high-dose chemotherapy with autologous stem cell support for non-lymphoid solid tumors. TEC Assessments. 1999;Volume 14:Tab 11. PMID


**Documentation for Clinical Review**

*Please provide the following documentation (if when requested):*

- 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
  - Specific issues identified during the transplant evaluation

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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. Inclusion or exclusion of codes does not constitute or imply member coverage or
provider reimbursement.

IE

The following services may be considered investigational.

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### Policy History

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

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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal 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.