

<b>8.01.24 Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults</b>			
<b>Original Policy Date:</b>	January 7, 2011	<b>Effective Date:</b>	April 1, 2024
<b>Section:</b>	11.0 Transplant	<b>Page:</b>	Page 1 of 19

**Policy Statement**

- I. Autologous or allogeneic hematopoietic cell transplantation is considered **investigational** for the following malignancies in adults:
  - A. Cancer of the bile duct
  - B. Cancer of the fallopian tubes
  - C. Cervical cancer
  - D. Colon cancer
  - E. Esophageal cancer
  - F. Gall bladder cancer
  - G. Lung cancer, any histology
  - H. Malignant melanoma
  - I. Nasopharyngeal cancer
  - J. Neuroendocrine tumors
  - K. Pancreatic cancer
  - L. Paranasal sinus cancer
  - M. Prostate cancer
  - N. Rectal cancer
  - O. Renal cell cancer
  - P. Soft tissue sarcomas
  - Q. Stomach cancer
  - R. Thyroid tumors
  - S. Tumors of the thymus
  - T. Tumors of unknown primary origin
  - U. Uterine cancer

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

**Policy Guidelines**

- N/A

**Description**

Hematopoietic cell transplantation (HCT) is an established treatment for certain hematologic malignancies and has been investigated for a variety of adult solid tumors. Interest continues in exploring nonmyeloablative allogeneic HCT (allo-HCT) for a graft-versus-tumor effect of donor-derived T-cells in metastatic solid tumors.

**Related Policies**

- Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma
- Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors

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## 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

Though cancer incidence along with overall mortality has been declining in the United States, certain population groups continue to have an increased risk of cancer progression and mortality due to social, economic, and environmental disadvantages.<sup>1</sup> The National Cancer Institute has published statistics on cancer disparities in relation to various criteria including specific racial and ethnic groups, gender, and geography. Some key incidence and mortality statistics in the United States are as follows: incidence rates of lung, colorectal, and cervical cancers are increased in rural Appalachia compared to urban areas; American Indians/Alaska Natives have increased mortality rates from kidney, liver, and intrahepatic bile duct cancer compared to other racial and ethnic groups; Black men are twice as likely to die of prostate cancer than White men.

### 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]). They 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. 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 the 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. After 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 normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

### **Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation**

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

### **Hematopoietic Cell Transplantation in Solid Tumors in Adults**

HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors is less well established, although it has been investigated for a variety of solid tumors. With the advent of nonmyeloablative allogeneic transplant, interest has shifted to exploring the generation of alloreactivity to metastatic solid tumors via a graft-versus-tumor effect of donor-derived T cells.<sup>2</sup>

HCT as a treatment for germ cell tumors, ependymoma, or malignant glioma is addressed separately in Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors and Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma, respectively). HCT as a treatment for breast cancer is not addressed. This evidence review collectively addresses other solid tumors of adults for which HCT has been investigated, including lung cancer, malignant melanoma, tumors of the gastrointestinal tract (affecting the colon, rectum, pancreas, stomach, esophagus, gallbladder, or bile duct), male and female genitourinary systems (e.g., renal cell carcinoma, prostate cancer, cervical cancer, uterine cancer, fallopian tube cancer), tumors of the head and neck, soft tissue sarcoma, thyroid tumors, tumors of the thymus, and tumors of unknown primary origin.

### **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, 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

## **Autologous Hematopoietic Cell Transplantation in Solid Tumors Adult Soft Tissue Sarcomas**

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

The purpose of autologous hematopoietic cell transplantation (HCT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with soft tissue sarcomas.

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

### ***Populations***

The relevant population of interest is adults with soft tissue sarcomas.

### ***Interventions***

The therapy being considered is autologous HCT.

### ***Comparators***

Comparators of interest include the standard of care.

### ***Outcomes***

The general outcomes of interest are overall survival (OS), disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

### **Study Selection Criteria**

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 events, 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

In general, the 5-year survival rate for soft-tissue sarcomas is over 65%. The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a 5-year survival estimate of 17%.<sup>3</sup> A variety of single-agent and combination regimens are used for treatment, with targeted therapies available for some subtypes.<sup>4</sup> Based on initial observations that patients who achieved complete remission (CR) had longer survival, several phase 1 and 2 trials using autologous HCT were conducted in the 1990s to improve outcomes.<sup>5</sup> These trials were composed of sample size ranging from 2 to 55, yielding overall response rates (ORRs) from 20% to 65%, with CR ranging from 10% to 43%. The longest reported 5-year progression-free survival (PFS) rate was 21%, and the 5-year OS rate was 32%.<sup>5</sup> One study of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease prior to HCT.<sup>6</sup> In another phase 2 study, 21 (38%) of 55 patients responded to doxorubicin-based induction chemotherapy, but estimated 5-year OS did not differ statistically between those who did (14%) and did not (3%) receive an autologous HCT ( $p=.08$ ).<sup>7</sup>

### Systematic Reviews

In 2017, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas.<sup>8</sup> One RCT assessing 83 patients was identified.<sup>9</sup> In the RCT, OS did not differ statistically between autologous HCT following high-dose and standard-dose chemotherapy (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.70 to 2.29;  $p=.44$ ), and the point estimate for survival at 3 years was 32.7% compared with 49.4%. Peinemann and Labeit (2014) conducted another systematic review that included an RCT (described above) and 61 single-arm studies.<sup>10</sup> The pooled risk of treatment-related mortality across 61 single-arm studies was 15 (5.1%) of 294 patients.

### Randomized Controlled Trials

A 2019 RCT evaluated the use of autologous HCT following high-dose chemotherapy for Ewing Sarcoma in patients younger than 50 years of age with only pulmonary or pleural metastases.<sup>11</sup> The median age of patients was 14.2 years (range, 1.0 to 47.8 years). Induction chemotherapy for all patients consisted of 6 chemotherapy courses combining vincristine, ifosfamide, doxorubicin, and etoposide and 1 course of vincristine, dactinomycin, and ifosfamide. Patients were then randomized to receive either high-dose chemotherapy with autologous HCT without whole-lung irradiation ( $n=144$ ) or standard-dose chemotherapy with whole-lung irradiation ( $n=143$ ). Median follow-up was 8.1 years. No significant differences in survival outcomes between treatment groups were observed. Event-free survival was 50.6% versus 56.6% at 3 years and 43.1% versus 52.9% at 8 years, for standard-dose chemotherapy and high-dose chemotherapy with autologous HCT, respectively (HR, 0.79; 95% CI, 0.56 to 1.10;  $p=.16$ ). The HR for OS was 1.00 (95% CI, 0.70 to 1.44;  $p=.99$ ). Four patients died as a result of toxicity from high-dose chemotherapy with autologous HCT, and none died after standard-dose chemotherapy. Investigators concluded there is no clear benefit from high-dose chemotherapy with autologous HCT compared with standard-dose chemotherapy.

### Nonrandomized Studies

Few studies not included in the Cochrane review have described outcomes after HCT for soft tissue sarcoma. Kasper et al (2010) reported the results of a prospective, single-institution phase 2 study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma.<sup>12</sup> After 4 courses of chemotherapy, 9 patients with at least a partial response underwent high-dose chemotherapy and autologous HCT. All other patients continued chemotherapy for 2 more cycles. Median PFS for patients treated with HCT was 11.6 months (range, 8 to 15 months) and 5.6 months for patients treated with standard chemotherapy ( $p=.047$ ); median OS for the 2 groups was 23.7 months (range, 12 to 34 months) and 10.8 months (range, 0 to 39 months;  $p=.027$ ), respectively.

Hartmann et al (2013) reported on results from a phase 2 study of high-dose chemotherapy with ifosfamide, carboplatin, and etoposide followed by peripheral blood stem cell transplantation in patients with grade 2 or 3 histologically proven soft tissue sarcoma considered unresectable or marginally resectable.<sup>13</sup> After a median follow-up of 50 months (range, 26 to 120 months) in surviving patients, median PFS for all patients was 21 months (range, 1 to 94 months) and median OS was 37 months (range, 3 to 120 months), corresponding to 5-year PFS and OS rates of 39% and 48%, respectively.

A 2020 registry study retrospectively evaluated the effectiveness of autologous HCT in the treatment of soft tissue sarcoma using data from the European Society for Blood and Marrow Transplantation database between 1996 and 2016 (N=338).<sup>14</sup> The PFS and OS were 8.3 and 19.8 months, respectively. The PFS and OS at 5 years were 13% and 25%, respectively. Predictors of favorable benefit with HCT were younger age, better remission status before transplantation, and melphalan-based preparative regimens. The authors concluded that autologous HCT should not be performed on patients with soft tissue sarcoma in routine clinical practice without further investigation.

### **Section Summary: Adult Soft Tissue Sarcomas**

Overall, 2 RCTs, several phase 2 studies, and a retrospective registry study have reported outcomes after autologous HCT in adults with soft tissue sarcoma. Although 1 phase 2 study reported longer survival for patients treated with HCT than with standard chemotherapy, the RCT did not show an OS benefit with autologous HCT. An RCT from 2019 also showed no survival benefits with autologous HCT.

### **Small Cell Lung Cancer**

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

The purpose of autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with small cell lung cancer (SCLC).

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

#### ***Populations***

The relevant population of interest is adults with SCLC.

#### ***Interventions***

The therapy being considered is autologous HCT.

#### ***Comparators***

Comparators of interest include the standard of care.

#### ***Outcomes***

The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

### **Study Selection Criteria**

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 events, 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

### Systematic Reviews

The interest in treating SCLC with autologous HCT stems from the extremely high chemosensitivity and poor prognosis of this tumor type. Jiang et al (2009) performed a meta-analysis of English-language studies through October 2008 using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC.<sup>15</sup> The meta-analysis consisted of 5 RCTs (3 phase 3 trials; 2 phase 2 trials), with a total of 641 patients. Reviewers found no significant increase in the odds ratio (OR) for response rate with autologous transplant versus control chemotherapy (OR, 1.29; 95% CI, 0.87 to 1.93;  $p=.206$ ). No statistically significant increase in OS was seen among the autologous transplant patients compared with control regimens (HR, 0.94; 95% CI, 0.80 to 1.10;  $p=.432$ ). Reviewers concluded that current evidence did not support the use of intensified chemotherapy and autologous HCT for treating SCLC.

### Randomized Controlled Trials

A phase 3 trial randomized 318 patients with SCLC to standard chemotherapy or to HCT.<sup>16</sup> No statistically significant difference in response rates was seen between the 2 groups (response rate, 80% in standard arm group vs. 88% in the HCT group; difference, 8%; 95% CI, -1% to 17%;  $p=.09$ ). There was no statistically significant difference in OS between groups, with a median OS of 13.9 months in the standard arm (95% CI, 12.1 to 15.7 months) and 14.4 months in the HCT arm (95% CI, 13.1 to 15.4 months;  $p=.76$ ). One randomized study and several single-arm studies of HCT and autologous HCT for SCLC are summarized in a 2007 review article.<sup>17</sup> Overall, most of the data from these studies, including the randomized study, showed no increase in OS with autologous HCT.

### Section Summary: Small Cell Lung Cancer

Treatment of SCLC with autologous HCT has been studied in a meta-analysis, RCTs, and case series. None of these studies showed a survival benefit with autologous HCT.

## Other Tumors

### Review of Evidence

Uncontrolled pilot studies of autologous HCT for patients with refractory urothelial carcinoma<sup>18</sup> and recurrent or advanced nasopharyngeal carcinoma<sup>19</sup> have not demonstrated adequate evidence of improved outcomes to alter previous conclusions. In a 2014 case series ( $n=8$ ) of bilateral retinoblastoma survivors with secondary osteosarcoma, 2 patients (of 7 treated with multimodal chemotherapy) received high-dose chemotherapy with autologous peripheral blood stem cell support.<sup>20</sup> The 2 HCT-treated patients were alive with no evidence of disease at 33.4 and 56.4 months of follow-up.

## Allogeneic Hematopoietic Cell Transplantation in Solid Tumors

The evidence base for the treatment of patients with other types of solid tumors (refractory urothelial carcinoma, recurrent or advanced nasopharyngeal carcinoma, and secondary osteosarcoma) using allogeneic HCT (allo-HCT) consists of single-case reports and case series.<sup>2,21,22</sup>

## Renal Cell Carcinoma

### Clinical Context and Therapy Purpose

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with renal cell carcinoma (RCC).

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

### *Populations*

The relevant population of interest is adults with RCC.

### *Interventions*

The therapy being considered is allo-HCT.

### **Comparators**

Comparators of interest include the standard of care.

### **Outcomes**

The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

### **Study Selection Criteria**

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 events, 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**

Metastatic RCC has an extremely poor prognosis, with a median survival of less than 1 year and 5-year survival of approximately 12%.<sup>23</sup> RCC is relatively resistant to chemotherapy, but is susceptible to immune therapy. Interleukin-2 and/or interferon- $\alpha$  have induced responses and long-term PFS rates in 4% to 15% of patients.<sup>22</sup> In addition, 10 targeted therapies are approved by the U.S. Food and Drug Administration for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, bevacizumab, cabozantinib, lenvatinib, and tivozanib.<sup>23</sup> Based on the susceptibility of RCC to immune therapies, the immune-based strategy of a graft-versus-tumor effect possible with an allogeneic transplant has led to an interest in its use in RCC. Childs et al (2000) published on the first series of patients with RCC treated with nonmyeloablative allo-HCT.<sup>24</sup> The investigators showed tumor regression in 10 (53%) of 19 patients with cytokine-refractory, metastatic RCC who received a human leukocyte antigen (HLA)-identical sibling allo-HCT. Three patients had a CR and remained in remission 16, 25, and 27 months after transplant. Four of 7 patients with a partial response were alive without disease progression 9 to 19 months after transplantation. Other pilot trials have demonstrated the graft-versus-tumor effect of allo-HCT in metastatic RCC, but most have not shown as high a response rate. Overall response rates in these pilot trials have been approximately 25%, with CR rates of approximately 8%.<sup>21</sup> Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC.<sup>21</sup>

Bregni et al (2009) assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received reduced-intensity conditioning (RIC) with allo-HCT from a sibling who was HLA-identical.<sup>25</sup> All patients received the same conditioning regimens. Response to allograft was available in 24 patients, with a CR in 1 patient and partial response in 4 patients. Twelve patients had a minor response or stable disease, and 7 had progressive disease. The overall response rate (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (range, 12 to 2332+ days). The 1-year OS rate was 48% (95% CI, 28% to 68%) and the 5-year OS rate was 20% (95% CI, 4% to 36%). The authors concluded that allografting can induce long-term disease control in a small fraction of cytokine-resistant patients with RCC, but that with the availability of novel targeted therapies for RCC, future treatment strategies should consider incorporating these therapies into the transplant regimen.

### **Section Summary: Allogeneic Hematopoietic Cell Transplantation in Renal Cell Carcinoma**

Evidence on the use of allo-HCT for RCC is based on multiple case series. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT results in improved OS among RCC patients.



## Colorectal Cancer

### Clinical Context and Therapy Purpose

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with colorectal cancer (CRC).

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

### *Populations*

The relevant population of interest is adults with CRC.

### *Interventions*

The therapy being considered is allo-HCT.

### *Comparators*

Comparators of interest include the standard of care.

### *Outcomes*

The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

## Study Selection Criteria

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 events, 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

Aglietta et al (2009) reported on their experience with 39 patients with metastatic CRC who underwent RIC allo-HCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation centers.<sup>26</sup> Patients were treated with 1 of 5 RIC regimens. Endpoints assessed were an achievement of mixed chimerism, the incidence of graft-versus-host disease (GVHD), treatment-related mortality, toxicities, OS, and time to treatment failure (in patients who responded to therapy). Patient population characteristics were heterogeneous; pretransplant disease status was a partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. Thirty-eight (97%) patients had previous treatment, some with only chemotherapy and others with surgery, chemotherapy, or both. After the transplant, tumor responses were complete and partial in 2% and 18% of patients, respectively, and 26% of patients had stable disease, for overall disease control in 46% of patients. Transplant-related mortality was 10%. Median overall follow-up was 202 days (range, 6 to 1020 days), after which time 33 patients had died and 6 were still alive. Tumor progression was the cause of death in 74% of patients. An assessment of the OS of patients was performed after stratifying by potential prognostic factors. Achievement of response after transplantation was associated with a difference in OS, with the 18 patients who had a response having a median OS of approximately 400 days versus approximately 120 days for those who had no response ( $p < .001$ ). The authors concluded the allo-HCT approach should be reserved for patients with a partial response or stable disease after second-line therapy for metastatic CRC and that second-generation clinical trials in these patients would be warranted.

**Section Summary: Allogeneic Hematopoietic Cell Transplantation in Colorectal Cancer**

Evidence on the use of allo-HCT for CRC is based on case series. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among individuals with CRC.

**Pancreatic Cancer****Clinical Context and Therapy Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with pancreatic cancer.

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

***Populations***

The relevant population of interest is adults with pancreatic cancer.

***Interventions***

The therapy being considered is allo-HCT.

***Comparators***

Comparators of interest include the standard of care.

***Outcomes***

The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

**Study Selection Criteria**

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 events, 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**

Kanda et al (2008) reported on the efficacy of RIC allo-HCT for advanced pancreatic cancer in 22 patients from 3 transplantation centers in Japan.<sup>27</sup> RIC regimens differed across centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 having locally advanced disease. All but 1 patient received chemotherapy of various combinations before a transplant, and 10 patients received localized radiotherapy. After allo-HCT, 1 patient achieved CR, 2 had a partial response, 2 had a minor response, and 8 had stable disease, with an ORR of 23%. Median survival was 139 days, and the major cause of death was tumor progression (median duration of survival in advanced pancreatic cancer in the nontransplant setting is less than 6 months, even in patients treated with gemcitabine). Only 1 patient survived longer than 1 year after transplantation. The authors concluded that tumor response was observed in 25% of patients with advanced pancreatic cancer who underwent allo-HCT and that the response was not durable. However, based on their observation of a relationship between longer survival and the infusion of a higher number of CD34-positive cells or the development of chronic GVHD, the authors recommended additional study to evaluate the immunologic effect on pancreatic cancer.

Abe et al (2009) reported on outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received nonmyeloablative conditioning with allo-HCT.<sup>28</sup> Median

age was 54 years (range, 44 to 62 years). All patients had advanced disease, either with metastases or peritonitis, and had received at least 1 course of chemotherapy including gemcitabine. After allo-HCT, tumor response was only observed in 2 patients; 1 had complete disappearance of the primary tumor and the other had a 20% reduction in tumor size; the remaining patients had progressive disease (n=2) or stable disease (n=1). Four patients died of progressive disease (median survival, 96 days; range, 28 to 209 days posttransplant). One patient died at day 57 secondary to rupture of the common bile duct from rapid tumor regression. The authors concluded that findings showed a graft-versus-tumor effect, but to obtain durable responses, an improved conditioning regimen and new strategies to control tumor growth after nonmyeloablative allo-HCT would be needed.

Omazic et al (2017) reported on outcomes for 2 patients who received allo-HCT from HLA-identical sibling donors following resection of pancreatic ductal adenocarcinoma.<sup>29</sup> These patients were compared with 6 controls who underwent radical surgery for pancreatic ductal adenocarcinoma but did not receive HCT. Both patients receiving HCT were tumor-free after 9 years following diagnosis, whereas all the patients in the control group died within 4 years of diagnosis.

### **Section Summary: Allogeneic Hematopoietic Cell Transplantation in Pancreatic Cancer**

Evidence on the use of allo-HCT for pancreatic cancer is based on multiple case series and a comparative study. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among individuals with pancreatic cancer.

### **Nasopharyngeal Cancer**

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

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with nasopharyngeal cancer.

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

#### ***Populations***

The relevant population of interest is adults with nasopharyngeal cancer.

#### ***Interventions***

The therapy being considered is allo-HCT.

#### ***Comparators***

Comparators of interest include the standard of care.

#### ***Outcomes***

The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

### **Study Selection Criteria**

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 events, 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

Toh et al (2011) reported on outcomes of a phase 2 trial of 21 patients with pretreated metastatic nasopharyngeal cancer.<sup>30</sup> Median patient age was 48 years (range, 34 to 57 years), and patients had received a median of 2 previous chemotherapy regimens (range, 1 to 8 regimens). All patients had extensive metastases. Patients underwent a nonmyeloablative allo-HCT with sibling allografts. Seven (33%) patients showed a partial response and 3 (14%) achieved stable disease. Four patients were alive at 2 years, and 3 showed prolonged disease control of 344, 525, and 550 days. After a median follow-up of 209 days (range, 4 to 1147 days), the median PFS was 100 days (95% CI, 66 to 128 days) and the median OS was 209 days (95% CI, 128 to 236 days). One- and 2-year OS rates were 29% and 19%, respectively, comparable to the median 7- to 14-month OS rates reported in the literature for metastatic nasopharyngeal patients treated with salvage chemotherapy without HCT.

### Section Summary: Allogeneic Hematopoietic Cell Transplantation in Nasopharyngeal Cancer

Evidence on the use of allo-HCT for nasopharyngeal cancer is based on a phase 2 trial. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among nasopharyngeal cancer patients.

### Mixed Tumor Types

#### Review of Evidence

Omazic et al (2016) reported on long-term follow-up for 61 patients with a variety of solid tumor types considered incurable with conventional therapies who were treated with allo-HCT from 1999 to 2012.<sup>31</sup> Tumors included metastatic renal carcinoma (n=22), cholangiocarcinoma (n=17), colon cancer (n=15), prostate cancer (n=3), pancreatic adenocarcinoma (n=3), and breast cancer (n=1). Most patients (n=59) had undergone surgical debulking of the primary tumor, and 31 patients had previously undergone additional therapy with cytotoxic chemotherapy, radiotherapy, or immunotherapy. Conditioning was myeloablative in 23 patients, reduced-intensity in 36 patients, and nonmyeloablative in 2 patients. Over a median follow-up of 8 years, OS rates at 5 and 10 years were 15% and 9%, respectively.

### 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.

### Practice Guidelines and Position Statements

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 the tumors addressed in this evidence review do not discuss hematopoietic cell transplantation (HCT) as a treatment option and these tumors are also not addressed in the NCCN HCT guideline.<sup>32,33</sup>

### American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) issued guidelines related to indications for autologous and allogeneic HCT.<sup>34</sup> The guidelines were updated in 2020.<sup>35</sup> The tumors addressed herein for which the Society has provided recommendations are listed in Table 1.

**Table 1. Recommendations for Use of Autologous and Allogeneic HCT**

Condition	Treatment Option	2015 Recommendation	2020 Recommendation
Ewing sarcoma, high-risk	Allogeneic HCT	Not generally recommended	Developmental
	Autologous HCT	Standard of care, clinical evidence available	Standard of care, clinical evidence available
Renal cancer, metastatic	Allogeneic HCT	Developmental	Developmental
	Autologous HCT	Not generally recommended	Not generally recommended

HCT: hematopoietic cell transplantation.

### 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: "Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT [autologous stem cell transplantation] for the following condition[s]: Solid tumors (other than neuroblastoma)."<sup>36</sup>

### Ongoing and Unpublished Clinical Trials

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

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04530487	Donor Stem Cell Transplant After Chemotherapy for the Treatment of Recurrent or Refractory High-Risk Solid Tumors in Pediatric and Adolescent-Young Adults	40	May 2025
NCT04937842	Efficacy and Safety of Radiotherapy or Chemotherapy Combined with Microtransplantation in the Treatment of Advanced and Relapsed Solid Tumors	60	June 2025
NCT01505569	Alkylator-Intense Conditioning Followed by Autologous Transplantation for Patients with High Risk or Relapsed Solid or CNS Tumors	20	March 2025

NCT: national clinical trial.

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## Documentation for Clinical Review

**Please provide the following documentation:**

- Referring provider history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - o Diagnosis (including disease staging) and prognosis
  - o Synopsis of alternative treatments performed and results
  - o Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - o Clinical history
  - o Specific issues identified during the transplant evaluation
  - o Consultation reports/letters (when applicable)
  - o Correspondence from referring providers (when applicable)
  - o 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:
  - o Chest x-ray (CXR)
  - o PET scan, CT scan, and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
  - o EKG
  - o Echocardiogram
  - o Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
  - o Bone marrow biopsy
  - o 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



Type	Code	Description
	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
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation	
HCPCS	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
03/30/2015	Policy revision without position change
04/01/2016	Policy revision without position change
03/01/2017	Policy title change from Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults Policy revision without position change
01/01/2018	Coding update
03/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
11/01/2019	Policy revision without position change
04/01/2024	Policy reactivated. Previously archived from 05/01/2020 to 03/31/2024.

## 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 and Feedback (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).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*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	
BEFORE	AFTER <u>Blue font: Verbiage Changes/Additions</u>
<p><b>Reactivated Policy</b></p> <p><b>Policy Statement:</b> N/A</p>	<p><b>Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults 8.01.24</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. Autologous or allogeneic hematopoietic cell transplantation is considered <b>investigational</b> for the following malignancies in adults:                             <ul style="list-style-type: none"> <li>A. Lung cancer, any histology</li> <li>B. Colon cancer</li> <li>C. Rectal cancer</li> <li>D. Pancreatic cancer</li> <li>E. Stomach cancer</li> <li>F. Esophageal cancer</li> <li>G. Gall bladder cancer</li> <li>H. Cancer of the bile duct</li> <li>I. Renal cell cancer</li> <li>J. Cervical cancer</li> <li>K. Uterine cancer</li> <li>L. Cancer of the fallopian tubes</li> <li>M. Prostate cancer</li> <li>N. Nasopharyngeal cancer</li> <li>O. Paranasal sinus cancer</li> <li>P. Neuroendocrine tumors</li> <li>Q. Soft tissue sarcomas</li> <li>R. Thyroid tumors</li> <li>S. Tumors of the thymus</li> <li>T. Tumors of unknown primary origin</li> <li>U. Malignant melanoma</li> </ul> </li> </ul>