I. 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 for a graft-versus-tumor effect of donor-derived T cells in metastatic solid tumors.

The evidence for HCT in individuals who have adult soft tissue sarcomas includes 2 TEC Assessments, 1 randomized controlled trial (RCT), and a number of phase 2 single-arm studies, a number of which have been summarized in a systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments focusing on HCT as primary and salvage therapy for a variety of solid tumors found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Although 1 small phase 2 study reported longer survival for patients treated with HCT than standard chemotherapy, this RCT did not show a survival benefit with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HCT in individuals who have small cell lung cancer (SCLC) includes 2 TEC Assessments, several RCTs, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments focusing on HCT as primary and salvage therapy for a variety of solid tumors found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Studies published since the TEC Assessments have not reported increased overall survival for patients with SCLC treated with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HCT in individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer includes a TEC Assessment and small single-arm series. Relevant
outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments focusing on HCT as primary and salvage therapy for a variety of solid tumors found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Since publication of the TEC Assessments, the evidence for HCT in cases of adult soft tissue sarcomas, renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

HEMATOPOIETIC CELL TRANSPLANTATION

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Conditioning for HCT

Conventional Conditioning

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is a result of a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.
The immune reactivity between donor T cells and malignant cells that is responsible for the GVM effect also leads to acute and chronic GVHD.

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

**Reduced-Intensity Conditioning for Allogeneic HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**HCT IN SOLID TUMORS IN ADULTS**

HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors is less well established. 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.

Hematopoietic SCT as a treatment of breast cancer, ovarian cancer, germ cell tumors, ependymoma, or malignant glioma is not addressed in this policy. This policy collectively addresses other solid tumors of adults for which HCT has been investigated, including lung cancer; malignant melanoma; tumors of the gastrointestinal tract (include colon, rectum, pancreas, stomach, esophagus, gallbladder, and bile duct); male and female genitourinary systems (e.g., renal cell carcinoma, cervical carcinoma, cancer of the uterus, fallopian tubes, and prostate gland); tumors of the head and neck; soft tissue sarcoma; thyroid tumors; tumors of the thymus; and tumors of unknown primary origin.
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 (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

II. Criteria/Guidelines
Autologous or allogeneic hematopoietic cell transplant is not covered for the following malignancies in adults as they are not known to improve health outcomes:
A. Lung cancer, any histology
B. Colon cancer
C. Rectal cancer
D. Pancreatic cancer
E. Stomach cancer
F. Esophageal cancer
G. Gall bladder cancer
H. Cancer of the bile duct
I. Renal cell cancer
J. Cervical cancer
K. Uterine cancer
L. Cancer of the fallopian tubes
M. Prostate cancer
N. Nasopharyngeal cancer
O. Paranasal sinus cancer
P. Neuroendocrine tumors
Q. Soft tissue sarcomas
R. Thyroid tumors
S. Tumors of the thymus
T. Tumors of unknown primary origin
U. Malignant melanoma

III. Administrative Guidelines

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<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
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<tr>
<td>38208</td>
<td>; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>HCPCS Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Q0083 - Q0085</td>
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<tr>
<td>J9000-J9999</td>
<td>Chemotherapy drugs code range</td>
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<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)</td>
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<table>
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<td>Administration, circulatory, transfusion, central vein, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
</tbody>
</table>
IV. Scientific Background

This policy was created based on a 1995 TEC Assessment (described next) and has been updated periodically with literature reviews through November 10, 2016.

This policy was initially based on a 1995 TEC Assessment that focused on adult solid tumors other than breast cancer, epithelial ovarian cancer, germ cell tumors, and glial cell–derived brain cancers. Solid tumors reported in the literature identified in the Assessment included lung cancers, melanoma, tumors of gastrointestinal organs, genitourinary system tumors, tumors of the head and neck, soft tissue sarcomas of the extremities and torso, thyroid tumors, tumors of the thymus, undifferentiated tumors, and tumors of unknown primary. The Assessment offered the following conclusions:

• While 125 articles were identified that reported on the results of HCT in a variety of solid tumors, only 17 included survival data from groups of patients with the same cancer. These studies reported on 4 indications: advanced small-cell lung cancer, advanced colorectal cancer, malignant melanomas, and inoperable gastric cancer.

• The evidence did not permit conclusions as to the effect of HCT on patient survival.

A 1999 TEC Assessment evaluated the use of allogeneic hematopoietic cell transplantation (allo-HCT) as a salvage therapy after a failed prior autologous HCT for solid tumors. Data were inadequate to permit conclusions.

AUTOLOGOUS HCT IN SOLID TUMORS OF ADULTS

The evidence on the use of autologous HCT for the solid tumors of adults addressed in this policy consists mainly of small series.

Adult Soft Tissue Sarcomas

The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a median survival of approximately 1 year and less than a 10% 5-year survival. A variety of single-agent and combination regimens are used for treatment, with targeted therapies available for
some subtypes. Based on initial observations that patients who achieved complete remission (CR) had longer survival; several Phase I and II trials using autologous HCT were conducted in the 1990s in an attempt to improve outcomes. These trials were composed of small numbers of patients (ranging from 2 to 55), yielding overall response rates from 20% to 65%, with CR from 10% to 43%. The longest reported 5-year progression-free survival (PFS) rate was 21%, and 5-year OS was 32%. One study of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease before undergoing HCT. In another Phase II study (2006), 21 of 55 (38%) patients responded to doxorubicin-based induction chemotherapy (14% vs. 3%; p=0.003), but estimated OS was not statistically different between those who received an autologous SCT and those who did not receive an autologous HCT (p=0.003).

In 2017, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy (HDC) for nonrhabdomyosarcoma soft tissue sarcomas. One RCT (2012) assessing 83 patients was identified. In the RCT, OS did not differ statistically between autologous HCT following HDC and standard-dose chemotherapy (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.70 to 2.29; p=0.44), and the point estimate for survival at 3 years was 32.7% compared with 49.4%. In 2014, Peinemann and Labeit conducted another systematic review that included an RCT (described above) and 61 single-arm studies. The pooled treatment-related mortality rate across 61 single-arm studies was 15 (5.1%) of 294.

A small number of studies not included in the Cochrane review have described outcomes after HCT for soft tissue sarcoma. Kasper and colleagues reported the results of a prospective, single institution phase 2 study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma. After 4 courses of chemotherapy, patients with at least a partial response underwent high-dose chemotherapy and autologous HCT (n=9). All other patients continued chemotherapy for 2 more cycles. The median PFS for patients treated with HCT was 11.6 months (range: 8 to 15 months) versus 5.6 months for patients treated with standard chemotherapy (p=0.047) and median OS for the 2 groups was 23.7 months (range: 12 to 34 months) versus 10.8 months (range: 0 to 39 months) (p=0.027), respectively.

Hartmann and colleagues reported results from a Phase II 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 that were considered unresectable or marginally resectable. After a median follow-up period of 50 months (range: 26 to 120 months) in surviving patients, the median PFS of all patients was 21 months (range: 1 to 94) 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 2014 case report of the use of autologous HCT for treatment of an adult histiocytic sarcoma was identified, in which the patient was alive with no evidence of disease 30 months post-treatment.

**Subsection Summary: Adult Soft Tissue Sarcomas**
Overall, one RCT and several small phase 2 studies have reported outcomes after autologous HCT in adult patients with soft tissue sarcoma. Although one small phase 2 study reported longer
survival for patients treated with HCT than standard chemotherapy, the available RCT did not show a survival benefit with HCT.

**Small Cell Lung Carcinoma**
The interest in treating small-cell lung carcinoma (SCLC) with HCT stems from the extremely high chemosensitivity and poor prognosis of this tumor type. A Phase III trial (2005) of 318 patients with SCLC randomly assigned patients to standard chemotherapy or HCT. No statistically significant difference in response rates was seen between the 2 groups (80% response rate in the standard arm vs. 88% in the HCT group [difference: 8%; 95% confidence interval (CI): -1% to 17%; p=0.09]). There was no statistically significant difference in OS between the 2 groups, with a median OS of 13.9 months in the standard arm (95% CI: 12.1 to 15.7 months) versus 14.4 months in the HCT arm (95% CI: 13.1 to 15.4 months; p=0.76). One smaller, randomized study and several single-arm studies of HCT and autologous HCT for SCLC are summarized in a review article. Overall, the majority of the data from these studies, including the randomized study, showed no increased OS with autologous HCT.

Jiang and colleagues (2009) performed a meta-analysis of English language studies through October 2008 using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC. The meta-analysis consisted of 5 randomized, controlled trials (RCTs; 3 were Phase III trials and 2 were Phase II), for a total of 641 patients. They found no significant increase in the odds ratio for response rate with autologous transplant versus control chemotherapy (odds ratio [OR] = 1.29; 95% CI: 0.87 to 1.93; p=0.206). No statistically significant increase in OS was seen among the autologous transplant patients compared to control regimens (HR = 0.94; 95% CI: 0.80 to 1.10; p=0.432). The authors concluded that current evidence does not support the use of intensified chemotherapy and autologous HCT for treating SCLC.

**Other Tumors**
Uncontrolled pilot studies of HCT for patients with refractory urothelial carcinoma and recurrent or advanced nasopharyngeal carcinoma failed to provide adequate evidence of improved outcomes to alter previous conclusions. In a 2014 small 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. The 2 HCT-treated patients were alive with no evidence of disease at 33.4 and 56.4 months of follow-up.

**Section Summary: Autologous HCT in Solid Tumors of Adults**
Since a 1995 TEC Assessment concluded that the evidence was insufficient to draw conclusions on HCT for lung cancers, melanoma, tumors of gastrointestinal organs, genitourinary system tumors, tumors of the head and neck, soft tissue sarcomas of the extremities and torso, thyroid tumors, tumors of the thymus, undifferentiated tumors, and tumors of unknown primary in adulthood, the largest body of evidence for autologous HCT in solid tumors in adults has been in sarcomas and SCLC. For both, meta-analyses of primarily retrospective data have shown no significant benefit from HCT. For other tumor types, the evidence is limited.
ALLOGENEIC HCT IN SOLID TUMORS OF ADULTS

Single-case reports and small series of patients with various types of solid tumors have been treated with allogeneic HCT, including some of the tumor types addressed in this policy.

Mixed Tumor Types

In 2016, Omazic et al reported on long-term follow-up for 61 patients with a variety of solid tumor types considered incurable with any conventional therapy who were treated with allo-HCT from 1999 to 2012.

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.

Renal Cell Carcinoma

Metastatic renal cell carcinoma (RCC) has an extremely poor prognosis, with a median survival of less than 1 year and a 5-year survival of less than 5%. RCC is relatively resistant to chemotherapy but is susceptible to immune therapy, and interleukin-2 (IL-2) and/or interferon alpha have induced responses and long-term PFS in 4% to 15% of patients. In addition, 7 targeted therapies are approved by the U.S. Food and Drug Administration for treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizumab. 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. In 2000, Childs and colleagues published the first series of patients with RCC treated with nonmyeloablative allogeneic HCT. The investigators showed regression of the tumor in 10 of 19 (53%) patients with cytokine-refractory, metastatic RCC who received an HLA-identical sibling allogeneic 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 allogeneic transplant in metastatic RCC, but most have not shown as high a response rate as the Childs and colleagues study. Overall response rates in these pilot trials have been approximately 25%, with CR rates of approximately 8%. Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC.

Bregni and colleagues (2009) assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received an RIC with allo-HCT from a sibling who is human leukocyte antigen (HLA) identical. 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 minor response or stable disease, and 7 had progressive disease. Overall response rate (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (12–2,332+). One-year OS was 48% (95% CI: 28 to 68), and
5-year OS was 20% (95% CI: 4 to 36). The authors concluded that allografting is able to 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 the incorporation of these therapies into the transplant regimen.

**Colorectal Cancer**

Aglietta and colleagues (2009) reported their experience with 39 patients with metastatic colorectal cancer who underwent reduced-intensity conditioning (RIC) allogeneic HCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation (EBMT) centers. Patients were treated with 1 of 5 different RIC regimens. Endpoints that were assessed were achievement of mixed chimerism, incidence (GVH), treatment-related mortality and toxicities, OS, and time to treatment failure (in patients who responded to the therapy). Patient population characteristics were heterogeneous; pre transplant disease status was partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. Thirty-eight patients (97%) had been previously treated, some with only chemotherapy and others with surgery and/or chemotherapy. After 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 1,020 days), after which time 33 patients had died and 6 were still alive. Tumor progression was the cause of death in 74% of patients. A comparison of OS of patients was performed after stratifying by some 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<0.001). The authors concluded that the HCT approach should probably be reserved for patients with a partial response or stable disease after second-line therapy for metastatic colorectal cancer and those second-generation clinical trials in these patients are warranted.

**Pancreatic Cancer**

Kanda and colleagues (2008) reported on the efficacy of RIC allogeneic HCT against advanced pancreatic cancer in 22 patients from 3 transplantation centers in Japan. The RIC regimens differed among the centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 locally advanced disease. All but 1 patient received chemotherapy of various combinations before transplant, and 10 patients received local radiation. After HCT, 1 patient achieved complete response, 2 patients had partial response, 2 had minor response, and 8 had stable disease, with an overall response rate 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 a tumor response was observed in one fourth of patients with advanced pancreatic cancer who underwent HCT and that the response was not durable. However, they felt that their observation of a relationship between longer survival and the infusion of a higher number of CD34-positive cells or the development of chronic graft-versus-host disease (GVHD) warrant future studies to enhance the immunologic effect against pancreatic cancer.
Abe and colleagues (2009) reported the outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative allogeneic peripheral blood HCT. The conditioning regimen consisted of fludarabine and low-dose total-body irradiation. The median patient 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 HCT, tumor response was only observed in 2 patients: 1 had complete disappearance of the primary tumor and 1 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, ranging from post-transplant day 28 to day 209 (median: 96 days). One patient died at day 57 secondary to rupture of the common bile duct from rapid tumor regression. The authors concluded that their study showed a graft-versus-tumor effect but that in order to obtain durable responses, an improved conditioning regimen and new strategies to control tumor growth after nonmyeloablative allogeneic HCT are needed.

Omazic et al (2017) reported on outcomes for 2 patients who received allo-HCT from human leukocyte antigen–identical sibling donors following resection of pancreatic ductal adenocarcinoma. 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.

Nasopharyngeal Cancer
Toh and colleagues (2011) reported the outcomes of a Phase II trial of 21 patients with pretreated metastatic nasopharyngeal cancer. 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). All patients had extensive metastases. Patients underwent a nonmyeloablative allogeneic HCT with sibling allografts. Seven patients (33%) 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 1,147 days), the median PFS was 100 days (95% CI: 66 to 128 days), and 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 months OS for metastatic nasopharyngeal patients in the literature treated with salvage chemotherapy without HCT.

SUMMARY OF EVIDENCE
For individuals who have adult soft tissue sarcomas who receive autologous hematopoietic cell transplantation (HCT), the evidence includes 2 TEC Assessments, 1 randomized controlled trial (RCT), and a number of phase 2 single-arm studies, some of which have been summarized in a systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on autologous HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Although 1 small phase 2 study
reported longer survival for patients treated with autologous HCT than with standard chemotherapy, this RCT did not show a survival benefit with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have small cell lung cancer (SCLC) who receive autologous HCT, the evidence includes 2 TEC Assessments, several RCTs, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on autologous HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Studies published since the TEC Assessments have not reported increased overall survival for patients with SCLC treated with autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes a TEC Assessment and small single-arm series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on allo-HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of allo-HCT on patient survival. Since publication of the TEC Assessments, the evidence for allo-HCT to treat adult soft tissue sarcomas, renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (2016-2017) on the tumors addressed in this evidence review do not discuss hematopoietic cell transplantation (HCT) as a treatment option.

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) issued guidelines related to indications for autologous and allogeneic HCT. The tumors addressed herein for which ASBMT has provided recommendations are as follows:

- Ewing sarcoma, high risk: allogeneic HCT – N (“not generally recommended”); autologous HCT – C (“standard of care, clinical evidence available”)

MEDICARE NATIONAL COVERAGE
The Centers for Medicare and 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).”

**Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

### Table 1. Summary of Key Trials

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NCT: national clinical trial.

V. **Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. **References**

3. 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.


