I. POLICY

Adoptive immunotherapy, using adoptive cellular therapy (ACT) for the administration of cytotoxic T-lymphocytes, cytokine-induced killer (CIK) cells, tumor-infiltrating lymphocytes (TIL), or antigen-loaded autologous dendritic cells (ADCs) or genetically engineered T cells is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Other applications of adoptive immunotherapy are considered investigational, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

Autologous lymphocytes used as part of adoptive immunotherapy may be harvested in a pheresis procedure or may be isolated from resected tumor tissue.

Cross-references:

MP-2.004 Donor Lymphocyte Infusion for Hematologic Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
MP-2.151 Cellular Immunotherapy for Prostate Cancer

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

ADOPTIVE IMMUNOTHERAPY

III. DESCRIPTION/BACKGROUND

Adoptive immunotherapy uses “activated” lymphocytes as a treatment modality. Both nonspecific and specific lymphocyte activation are used therapeutically. Nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes. Initially, this was done by harvesting peripheral lymphokine-activated killer cells and activating them in vitro with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. Expansion of TIL for clinical use is labor intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases. These factors limit the widespread applicability of TIL treatment. Recently, cytokine-induced killer cells have been recognized as a new type of antitumor effector cells, which can proliferate rapidly in vitro, with stronger antitumor activity and a broader spectrum of targeted tumors than other reported antitumor effector cells.1

The major research challenge in adoptive immunotherapy is to develop immune cells with antitumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, 2 methods are studied: adoptive cellular therapy (ACT) and antigen-loaded dendritic cell infusions.

ACT is “the administration of a patient’s own (autologous) or donor (allogeneic) anti-tumor lymphocytes following a lymphodepleting preparative regimen.”2 Protocols vary, but include these common steps:

1. lymphocyte harvesting (either from peripheral blood or from tumor biopsy)
2. propagation of tumor-specific lymphocytes in vitro using various immune modulators
3. selection of lymphocytes with reactivity to tumor antigens with ELISA
4. lymphodepletion of the host with immunosuppressive agents
5. adoptive transfer (i.e., transfusion) of lymphocytes back into the tumor-bearing host

Dendritic cell-based immunotherapy uses autologous dendritic cells (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then retransfused into the patient, where they present antigen to effector lymphocytes (CD4+ T cells, CD8+ T cells, and in some cases, B cells). This initiates a cytotoxic response against the antigen and against any cell expressing the antigen. In cancer immunotherapy, ADCs are pulsed with tumor antigens; effector lymphocytes then mount a cytotoxic response against tumor cells expressing these antigens. (See Related Policies links for dendritic cell-based immunotherapy for prostate cancer.)
In an attempt to further regulate the host immune system, recent protocols use various cytokines (e.g., IL-7 and IL-15 instead of IL-2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

Note: Allogeneic stem cell transplantation following nonmyeloablative conditioning of the recipient (known as reduced-intensity conditioning [RIC]) also may be referred to as “adoptive immunotherapy” in the literature. However, RIC stem cell transplantation relies on a donor-versus-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this evidence review enhance autoimmune effects primarily. The use of RIC in stem cell transplantation is discussed for specific cancers in individual policies related to stem cell transplantation.

**Regulatory Status**

Adoptive immunotherapy is not a U.S. Food and Drug Administration–regulated procedure.

### IV. RATIONALE

The most recent literature search was performed for the period through November 10, 2015. Adoptive immunotherapy has been investigated for treatment of relatively common cancers in which novel treatments have been adopted when randomized clinical trials show efficacy. The selected studies included only new randomized clinical trials.

**Systematic Reviews of Adoptive Immunotherapy Modalities**

Three systematic reviews on adoptive immunotherapy combining studies using different adoptive immunotherapy methods have been published. Conditions treated in these reviews were renal cell carcinoma, and postoperative hepatocellular carcinoma.

**Renal Cell Carcinoma**

In 2013, Tang et al published a meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy of adoptive immunotherapy in patients with metastatic renal cell carcinoma. Four RCTs (3 studies published between 1990 and 1999, a fourth study by Liu et al published in 2012 [discussed below]) met inclusion criteria (total N=469); 3 RCTs were conducted in the United States and one was conducted in China. Interventions included cytokine-induced killer (CIK) cells, lymphokine-activated killer (LAK) cells, and tumor-infiltrating lymphocytes (TIL). Most adoptive immunotherapy–related adverse reactions were grade 1 or 2 and reversible. In meta-analysis, outcomes were superior for patients treated with adoptive immunotherapy compared with no adoptive immunotherapy, including rates of objective response (pooled risk ratio [RR], 1.65; 95% confidence interval [CI], 1.15 to 2.38; \( p=0.007 \); \( I^2=49\%\)), 1-year survival (pooled RR=1.30; 95% CI, 1.12 to 1.52; \( p<0.001 \); \( I^2=0\%\)), 3-year survival (RR=2.76; 95% CI, 1.85 to 4.14; \( p<0.001 \); \( I^2=46\%\)), and 5-year survival (RR=2.42; 95% CI, 1.21 to 4.83; \( p=0.01 \); \( I^2=28\%\)). Heterogeneity across studies was acceptable. However, limitations of the review included varying adoptive immunotherapy protocols and lack of clear...
descriptions of randomization methods, allocation concealment, blinding, and withdrawals, which may lead to distribution and implementation bias in this meta-analysis.

**Hepatocellular Carcinoma**

Xie et al (2012) performed a meta-analysis of RCTs comparing adoptive immunotherapy with no adjuvant treatment in patients with hepatocellular carcinoma who had undergone curative resection. Six RCTs (published between 1995 and 2009; total N=494) met inclusion criteria. All 6 trials were conducted in Asia (4 in China, 2 in Japan), with 2 studies published in the Chinese language. Two trials used CIK cells as adoptive immunotherapy, 1 used CIK cells plus interleukin-2 (IL-2), and the remaining 3 used LAK plus IL-2. Outcome measures were 1- and 3-year recurrence and survival rates. Meta-analysis revealed a significantly reduced risk of both 1-year recurrence (odds ratio [OR], 0.35; 95% CI, 0.17 to 0.71; p=0.003), and 3-year recurrence (OR=0.31; 95% CI, 0.16 to 0.61; p=0.001) in patients receiving adoptive immunotherapy. However, no statistically significant difference was observed in 3-year survival rates between the 2 study groups (OR=0.91; 95% CI, 0.45 to 1.84; p=0.792). It is difficult to reach any conclusions regarding the results of this meta-analysis given the treatment context of the studies, variation in immunotherapy regimens, limited sample size and follow-up period, and low-to-moderate methodological quality of the included trials.

Zhong et al (2012) also performed a systematic review of RCTs to evaluate the clinical efficacy of adjuvant adoptive immunotherapy for postoperative patients with hepatocellular carcinoma. Four RCTs (published between 1995 and 2009; total N=423) met inclusion criteria. As with the Xie meta-analysis discussed above, all 4 trials were conducted in Asia. Three (of 4) trials in this review also were included in the Xie meta-analysis. Primary outcomes evaluated in this review were overall survival (OS), disease-free survival (DFS), and recurrence rates. The secondary outcome was adverse effects of treatment/toxicity. Owing to clinical heterogeneity (including operation methods, dose, and type of cytokines) across studies, meta-analysis was not performed. All RCTs reported significantly improved DFS or reduced recurrence rate after treatment with adjuvant adoptive immunotherapy (p<0.05). However, no statistically significant differences were observed in OS between study groups across the 3 trials reporting this outcome. The main adverse effect of adoptive immunotherapy was fever (persistent or transient), reported in 3 (of 4) trials. Conclusions of this systematic review are subject to similar limitations as with the above meta-analysis by Xie et al.

**Section Summary: Systematic Reviews of Adoptive Immunotherapy Modalities**

Three systematic reviews evaluating RCTs provide limited evidence for improved health outcomes with adoptive immunotherapy due to heterogeneity of adoptive immunotherapy methods, low methodological quality of included trials, and restricted applicability of the findings. In hepatocellular carcinoma, recurrence rates and DFS were improved with various adoptive immunotherapy treatments (CIK cells ± IL-2, LAK cells) compared with controls, but not OS. In renal cell carcinoma, objective response and 1-, 3-, and 5-year survival was improved with various adoptive immunotherapy treatments (CIK cells, LAK cells, TILs) compared with controls.
Cytotoxic T Lymphocytes

Epstein-Barr Virus–Associated Cancers
Bollard et al (2014) conducted an international prospective cohort study of cytotoxic T lymphocytes (CTL) therapy in patients with Epstein-Barr virus (EBV)–positive Hodgkin or non-Hodgkin lymphoma. Patients had either active, relapsed disease (n=21) or were in remission with high risk of relapse (n=29). CTLs with activity against EBV antigens were generated by incubating peripheral blood monocytes with EBV antigen-infected dendritic cells. Eleven (52%) of 21 patients with active disease achieved complete response, and 2 patients (10%) achieved partial response; 2-year event-free survival in this cohort was approximately 50%. Twenty-seven (93%) of 29 patients in remission achieved complete response; 2-year event-free survival was 82%. Immediate or delayed toxicity related to CTL infusion was not observed.

Chia et al (2014) studied 35 patients with EBV-positive nasopharyngeal cancer at a single center in China. Patients received standard chemotherapy with gemcitabine and carboplatin followed by EBV-specific CTL infusion. Median progression-free and OS were 8 months and 30 months, respectively. One-, 2-, and 3-year OS was 77%, 63%, and 37%, respectively. In comparison, median OS in a group of similar historical controls treated at the same institution with chemotherapy only was 18 to 21 months, and 2- and 3-year OS was 30% to 43% and 16% to 25%, respectively. The most common adverse events associated with CTL infusion were grade 1 and 2 fatigue and grade 1 myalgia. Two patients developed transient fever, and 3 patients developed grade 1 skin rash. Grade 3 or higher hematological or nonhematological toxicities were not observed during CTL therapy. In a Japanese series of 7 patients who received CTLs for advanced oral and maxillofacial cancers, 1-year survival in patients who achieved response (n=3) and in those with progressive disease (n=4) were 100% and 25%, respectively, although definitions of response were unclear.

Cytomegalovirus-Associated Cancers
Schuessler et al (2014) administered CTLs with or without chemotherapy to 13 patients with recurrent glioblastoma multiforme. CTLs with activity against cytomegalovirus were generated by incubating peripheral blood monocytes with synthetic peptide epitopes. Median OS was 1.1 years (range, 4.4 months to 6.6 years). Adverse events were minor.

Section Summary: Cytotoxic T Lymphocytes
Small, prospective cohort studies in patients with relapsed disease indicated response to infused CTLs directed against cancer-associated viral antigens. Adverse events were mild or moderate. Although a single-center study in Chinese patients with nasopharyngeal cancer reported improved survival compared with historical controls, RCTs are needed to demonstrate net health benefit of CTL therapy.

Cytokine-Induced Killer Cells

Nasopharyngeal Carcinoma
Li et al (2012) conducted an RCT to evaluate the efficacy of autologous CIK transfusion in combination with gemcitabine and cisplatin (GC) chemotherapy to treat nasopharyngeal
carcinoma in patients with distant metastasis after radiotherapy. \textsuperscript{10} From September 2007 to August 2008, 60 patients with distant metastasis after radiotherapy were followed up in a university cancer center in China. Patients were randomly divided into 2 groups; 30 patients in the GC+CIK group received adoptive autologous CIK cell transfusion in combination with GC chemotherapy, and 30 patients in the GC group received chemotherapy alone. One- and 2-year OS were 90\% (27/30) and 70\% (21/30), respectively, in the GC+CIK group versus 83\% (25/30) and 50\% (15/30), respectively, in the GC group. Mean OS was 31 months for the GC+CIK group and 26 months for the GC group (log-rank test, p=0.137). Median PFS was 26 months for the GC+CIK group and 19 months for the GC group (log-rank test, p=0.023). This small, single-center RCT indicates that the combination of CIK cells and GC regimen chemotherapy may be a viable treatment option for patients with advanced nasopharyngeal carcinoma. \textsuperscript{10}

**Renal Cell Carcinoma**

Liu et al (2012) conducted an RCT to evaluate the effects of autologous CIK cell immunotherapy in patients with metastatic renal cell carcinoma followed up in another university cancer center in China. \textsuperscript{11} From June 2005 to June 2008, 148 patients were randomized to autologous CIK cell immunotherapy (arm 1, n=74) or IL-2 treatment combination with human interferon-alfa-2a (arm 2, n=74). The primary end point was OS, and the secondary end point was PFS evaluated by Kaplan-Meier analyses and hazard ratios (HRs) with Cox proportional hazards models. Three-year PFS and OS in arm 1 were 18\% and 61\%, respectively, versus 12\% and 23\%, respectively, in arm 2 (p=0.031 and <0.001, respectively). Median PFS and OS in arm 1 were significantly longer than those in arm 2 (PFS, 12 vs 8 months, p=0.024; OS, 46 vs 19 months, p<0.001). Multivariate analyses indicated that the cycle count of CIK cell immunotherapy as a continuous variable was significantly associated with prolonged PFS (HR=0.88; 95\% CI, 0.84 to 0.93; p<0.001) and OS (HR=0.58; 95\% CI, 0.48 to 0.69; p<0.001) in arm 1. These findings suggest that CIK cell immunotherapy has the potential to improve the prognosis of patients with metastatic renal cell carcinoma. \textsuperscript{11}

Zhang et al (2013) conducted a small RCT in China with 20 patients who had unilateral, locally advanced renal cell carcinoma after nephrectomy. \textsuperscript{12} Patients were randomized 1:1 to postoperative CIK therapy or usual care (chemotherapy with or without radiation therapy, additional surgery, or no further treatment). Method of randomization was not described. At a median follow-up of 44 months, 6 patients in the CIK group and 5 controls achieved complete response; 2 patients in the CIK group and no controls achieved partial response (overall objective response, 80\% vs 50\% in the CIK and control groups, respectively; Fisher exact test, p=0.175). Mean PFS was significantly longer in the CIK group, but OS was not (mean PFS, 32 months vs 22 months; log-rank test, p=0.032; mean OS, 35 months vs 34 months; log-rank test, p=0.214). Adverse events included mild arthralgia, laryngeal edema, fatigue, and low-grade fever in 3 patients. Grade 3 or higher adverse events were not observed.

Zhao et al (2015) conducted an RCT in China among operable and inoperable patients with renal cell carcinoma. \textsuperscript{13} Dendritic cells were also incorporated into treatment. Among the 60 operable patients, the 3-year DFS was 96.7\% compared with 57.7\% in the control group. PFS was also
better in the CIK group (p=0.021). Among the 62 inoperable patients, OS was better in the CIK group (p=0.012). There were no severe adverse reactions observed.

**Gastric Cancer**

In 2012, Shi et al in China published a nonrandomized, comparative study to determine the long-term efficacy of adjuvant immunotherapy with autologous CIK cells in 151 patients with locally advanced gastric cancer. \(^{14}\) Five-year OS and 5-year DFS for immunotherapy versus no immunotherapy (control group) were 32% versus 23% (p=0.07) and 28% versus 10% (p=0.04), respectively. For patients with intestinal-type tumors, 5-year OS and DFS were significantly higher for immunotherapy (OS, 47% vs 31%; p= 0.045; DFS, 42% vs 16%; p=0.02).\(^{14}\) Larger and well-designed multicenter studies are needed to confirm these findings.

**Hepatocellular Carcinoma**

Yu et al (2014) conducted an RCT in China of 132 patients who had previously untreated hepatocellular carcinoma. \(^{15}\) Patients were randomized 1:1 to receive CIK therapy plus standard treatment (surgical resection in eligible patients, local treatment, or best supportive care) or standard treatment only. At a median follow-up of 19 months, median PFS was 14 months in the CIK group versus 7 months in the control group (log-rank test for all comparisons, p=0.019). Estimated 1-, 2-, and 3-year PFS was 56% versus 35% (p=0.004), 36% versus 18% (p=0.004), and 27% versus 18% (p=0.017), respectively. Median OS was 25 months in the CIK group versus 11 months in the control group (p=0.008). Estimated 1-, 2-, and 3-year OS was 74% versus 50% (p=0.002), 53% versus 30% (p=0.002), and 42% versus 24% (p=0.005), respectively. In the subgroup of operable patients, 3-year and median OS did not differ statistically between groups. Common adverse events attributed to CIK therapy were grade 1 or 2 fever, allergy, and headache. Grade 3 or 4 adverse events were not observed. A nonrandomized study from China reported improved PFS in 30 patients who received radiofrequency ablation plus CIK/natural killer cell/gamma delta T-cell (a type of TIL) infusion (median PFS, not reached) compared with 32 patients who received radiofrequency ablation alone (median PFS=12.0 months).\(^{16}\)

Lee et al (2015) conducted an RCT in Korea of 230 patients being treated for hepatocellular carcinoma by surgical resection, radiofrequency ablation, or percutaneous ethanol injection. \(^{17}\) Patients were randomized 1:1 to receive adjuvant CIK cell injections 16 times during 60 weeks or no adjuvant therapy. The primary end point was recurrence-free survival; secondary end points included OS and cancer-specific survival. The median recurrence-free survival was 44 months in the CIK group and 30 months in the control group (p=0.010). OS was longer in the CIK group than in the control group (HR=0.21, p=0.008). Cancer-specific survival was longer in the CIK group than in the control group (HR=0.19, p=0.02). Adverse events occurred more frequently in the CIK group than in the control group, but grade 3 or 4 adverse events did not differ significantly between groups. Adverse reactions associated with CIK included pyrexia, chills, myalgia, and fatigue.
Non-Small-Cell Lung Cancer

Wang et al (2014) conducted a systematic review of RCTs of CIK cells for the treatment of non-small-cell lung cancer (NSCLC). Overall, 17 RCTs (total N=1172 patients) were included in the analysis. The studies generally had small sample sizes; the largest had 61 CIK-treated patients and 61 control patients. Most studies also incorporated dendritic cell therapy. All were conducted in China. A significant effect of CIK was found for median time to progression and median survival time. OS at various time points significantly favored CIK.

Section Summary: Cytokine-Induced Killer Cells

Several RCTs from Asia have evaluated the efficacy of CIK cells in different cancer types. These studies have generally reported some benefits in recurrence rates and/or DFS. Several studies of different cancer types report improved OS. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses.

Tumor-Infiltrating Lymphocytes

Melanoma

Dudley et al (2008) conducted a series of nonrandomized phase 2 studies examining TIL plus IL-2 in patients with metastatic melanoma under various conditions of preinfusion lymphodepletion. A nonmyeloablative 7-day chemotherapy regimen (n=43) was compared with ablative regimens comprising 5-day chemotherapy plus either 200 cGy (n=25) or 1200 cGy (n=25) total-body irradiation. Ninety-five percent of patients had progressive disease after prior systemic treatment. Objective response rates by Response Evaluation Criteria in Solid Tumors (RECIST) were 49%, 52%, and 72%, respectively, and did not differ significantly among groups. Responses occurred at multiple metastatic sites, including brain, and many were durable; 10 patients who achieved complete response had no relapse at a median follow-up of 31 months. Toxicities of treatment occurred primarily in the 1200 cGy group and included a delay in marrow recovery of 1 to 2 days compared with the other treatment groups, somnolence requiring intubation, renal insufficiency, and posterior uveitis. Rosenberg et al (2011) reported updated results of these patients with median follow-up of 62 months. Ten patients who previously had been classified as partial responders were reclassified as complete responders by RECIST (1, 3, and 6 patients in the nonmyeloablative, 200 cGy, and 1200 cGy groups, respectively). Of these 20 patients (22% of the original cohort), 19 (95%) had ongoing complete regression longer than 3 years. Actuarial 3- and 5-year survival for the entire group was 36% and 29%, respectively, but for the 20 complete responders, 100% and 93%, respectively. Likelihood of achieving a complete response was similar regardless of prior therapy.

Dreno et al (2002) conducted an RCT of 88 patients with malignant melanoma without detectable metastases who were randomized to receive TIL plus IL-2 versus IL-2 alone. There was no significant difference in the duration of relapse-free interval or OS. Figlin et al (1999) randomized 178 patients with metastatic renal cell carcinoma or resectable renal tumors to adjuvant continuous low-dose IL-2 therapy, with or without additional TIL. TILs were
harvested from surgical specimens. Outcomes were similar in both groups, and for this reason the trial was terminated early.

Section Summary: Tumor-Infiltrating Lymphocytes
One small RCT compared TILs plus IL-2 with IL-2 alone in patients with nonmetastatic melanoma and reported no difference between treatment groups in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma demonstrated response rates of 49% and 52% to 72% with TIL plus nonmyeloablative or myeloablative regimens, respectively. Durable responses in the majority of patients who achieved complete response were observed beyond 3 years. Toxicities appeared primarily associated with myeloablative regimen. Definitive RCTs showing treatment benefit are needed to establish efficacy.

Dendritic Cells
Antigen-loaded autologous dendritic cells (ADCs) have been explored primarily in early-stage trials in various malignancies including lymphoma, myeloma, subcutaneous tumors, melanoma, NSCLC, renal cell cancer, and cervical cancer. A 2012 review article highlighted progress in dendritic cell-based immunotherapy in epithelial ovarian cancer.

Glioblastoma Multiforme
In 2013, Bregy et al published a systematic review of observational studies of active immunotherapy using ADCs in the treatment of glioblastoma multiforme. Twenty-one studies published through early 2013 were included in this review (total N=403). Vaccination with dendritic cells loaded with autologous tumor cells resulted in increased median OS in patients with recurrent disease (72-138 weeks across 8 studies), as well as in those newly diagnosed (65-230 weeks across 11 studies) compared with average survival of 58 weeks. Complications and safety of the vaccine were assessed in all studies. No study indicated any sign of autoimmune reaction. The majority of adverse events were injection site reactions (22%). Other adverse events included fatigue (19.5%), constipation/diarrhea (1.6%), myalgia/malaise (1.6%), shivering (1.4%), and vomiting (0.5%). Because of the nature of the current literature available (i.e., case reports, phase 1 and phase 2 clinical trials, prospective studies), the review is subject to publication and selection bias, which has the potential to lessen or amplify the true potential of adoptive immunotherapy. Larger controlled trials are required to assess survival and effect on quality of life of adoptive immunotherapy in this patient population.

Non-Small-Cell Lung Cancer
Shi et al (2012) conducted an RCT at a university cancer center in China to evaluate the role of dendritic cell (DC)/CIK combination immunotherapy as maintenance treatment of advanced NSCLC. From October 2008 to June 2010, 60 patients with stage IIIB/IV disease after treatment with 4 cycles of a platinum-based chemotherapy regimen were randomly divided into 2 groups. One group was treated with DC/CIK cell therapy (n=30), and the other was a control group who received no adoptive immunotherapy (n=30). Outcome measures were PFS and adverse effects of treatment/toxicity. PFS was 3.2 months in the DC/CIK group (95% CI, 2.9 to 3.5) versus 2.6 months control group (95% CI, 2.39 to 2.73; p<0.05). No significant toxic reactions were observed in the DC/CIK group, including bone marrow toxicity and
gastrointestinal reactions. The findings of this small single-center RCT indicate that combination immunotherapy with dendritic cells and CIK cells may offer a viable option as maintenance therapy for patients with advanced NSCLC.\textsuperscript{28}

Chen et al (2014) in China conducted a systematic review and meta-analysis of RCTs that compared DC/CIK combination immunotherapy with any other treatment (placebo, no intervention, conventional treatment, or other complementary and alternative medicines) for any cancer type and stage.\textsuperscript{34} Two included RCTs that compared DC/CIK plus chemotherapy with chemotherapy alone in patients with stage III/IV NSCLC reported OS estimates (total N=150). Pooled RRs favored DC/CIK therapy at 2 years but not at 1 year (RR for 1-year OS=1.38; 95\% CI, 1.00 to 1.90; \textit{p}=0.05; \textit{I}^2=35\%; RR for 2-year OS=2.88; 95\% CI, 1.38 to 5.99; \textit{p}=0.005; \textit{I}^2=0\%).

The systematic review by Wang et al mentioned previously included many studies that used DC in combination with CIK.\textsuperscript{18}

**Medullary Thyroid Cancer**

In a 2009 phase 1 pilot study, 10 patients with metastatic medullary thyroid cancer (MTC) were treated with ADCs pulsed with allogeneic MTC tumor cell lysate.\textsuperscript{35} At median follow-up of 11 months, 3 patients (30\%) had stable disease and 7 patients (70\%) progressed. No World Health Organization grade 3 or 4 toxicities or autoimmune reactions were observed. Of note, human leukocyte antigen match between patients and tumor cell lines did not predict disease stabilization or progression, suggesting that, should future studies demonstrate efficacy of ADC therapy for MTC using allogeneic tumor lysate, an unlimited source of tumor material may be available for lysate preparation.

**Pancreatic Cancer**

A 2009 phase 1 study of 5 patients with inoperable pancreatic cancer reinfused ADCs and LAK cells with gemcitabine; antigen priming of the ADCs was presumed to occur in vivo from apoptosis of gemcitabine-exposed tumor cells.\textsuperscript{36} One patient had a partial response, 2 had stable disease for more than 6 months, and 2 patients had disease progression. Toxicities included grade 1 anemia and grade 2 leukocytopenia, nausea, and constipation.

**Section Summary: Dendritic Cells**

Observational studies and small RCTs have examined the role of adoptive immunotherapy with ADCs in glioblastoma multiforme, NSCLC, medullary thyroid cancer, and pancreatic cancer. All patients had advanced disease; however, treatment protocols varied across studies (e.g., coadministration with other types of primed cells and/or chemotherapy). Treatment-associated toxicities were generally acceptable, but response rates varied across cancer types. The RCT in patients with NSCLC showed increased PFS with ADC/CIK adoptive immunotherapy compared with controls. Although results of this RCT and of some observational studies (e.g., in glioblastoma multiforme) are encouraging, the overall body of evidence does not demonstrate improved net health outcome in any of the cancers studied.
Genetically Engineered T Cells

Engineered T cell–based antitumor immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors (CAR). Review articles have highlighted recent progress in this field for solid and hematologic malignancies.37-39

TCR Therapy
In a phase 2 study, Johnson et al (2009) transfected autologous peripheral lymphocytes of 36 patients who had metastatic melanoma with genes encoding TCRs highly reactive to melanoma/melanocyte antigens (MART-1:27-35 and gp100:154-162).40 Nine patients (25%) experienced an objective response; 8 patients had a partial response lasting 3 months to more than 17 months; and 1 patient (in the gp100 group) had a complete response lasting more than 14 months. Treatment toxicities included erythematous rash, anterior uveitis, hearing loss, and dizziness, suggesting that these were attributable to recognition by the genetically modified lymphocytes of normally quiescent cells expressing the targeted cancer antigens; melanocytic cells exist in the skin, eye, and the inner ear. Ideal targets for TCR gene therapy may be antigens that arise in cancers of nonessential organs (e.g., prostate, ovary, breast, thyroid) or are not expressed on normal adult tissues (e.g., cancer-testes antigens).

Additional studies have examined TCR gene therapy in Hodgkin41 and non-Hodgkin lymphoma,42 prostate tumors,43 and neuroblastoma.44

CAR Therapy
CAR therapy generates T cells that express artificial TCRs that bind tumor cell surface antigens but do not need to match the patient’s immune type.39 Preliminary U.S. studies have investigated add-on CAR therapy in 8 patients with relapsed chronic lymphocytic leukemia.45,46 Four (50%) of 8 patients achieved complete remission. Adverse events included significant cytokine-mediated toxicities (fever, hypotension, and mental status changes) requiring high-dose, lymphotoxic steroid therapy in 3 patients who had high tumor burden at the time of CAR therapy.

Section Summary: Genetically Engineered T Cells
One small cohort study in patients with metastatic melanoma reported a 25% response rate with TCR gene therapy and broad treatment-related toxicities. This evidence does not demonstrate net health benefit with genetically engineered T cells in patients with metastatic melanoma. CAR therapy is in a preliminary stage of development.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.
Table 1. Ongoing Adoptive Immunotherapy Randomized Controlled Trials Listed at ClinicalTrials.gov

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<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT01691664</td>
<td>Adoptive Cellular Therapy and Radiation Therapy After Surgery in Treating Patients With Esophageal Cancer</td>
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<td>NCT02118415</td>
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<td>NCT02229266</td>
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<td>NCT01319565</td>
<td>Prospective Randomized Study of Cell Therapy for Metastatic Melanoma Using Short-Term Cultured Tumor Infiltrating Lymphocytes Plus IL-2 Following Either a Non-Myeloablative Lymphocyte Depleting Chemotherapy Regimen Alone or in Conjunction w/1200 TBI</td>
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<td>Jun 2020</td>
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<td>NCT01966289</td>
<td>SGI-110 in Combination With an Allogeneic Colon Cancer Cell Vaccine (GVAX) and Cyclophosphamide (CY) in Metastatic Colorectal Cancer (mCRC)</td>
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<td>Dec 2017</td>
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<tr>
<td>NCT01993719</td>
<td>A Phase II Prospective Randomized Study of Cell Transfer Therapy for Metastatic Melanoma Using Tumor Infiltrating Lymphocytes Plus IL-2 Comparing Two Different Chemotherapy Preparative Regimens</td>
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<td>NCT00045968</td>
<td>Study of a Drug [DCVax®-L] to Treat Newly Diagnosed GBM Brain Cancer</td>
<td>348</td>
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<td>NCT00335377</td>
<td>Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization</td>
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<td>NCT01204684</td>
<td>Dendritic Cell Vaccine for Patients With Brain Tumors</td>
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<td>NCT01280552</td>
<td>A Study of ICT-107 Immunotherapy in Glioblastoma Multiforme (GBM)</td>
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<td>NCT01691625</td>
<td>Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer</td>
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<td>Adoptive Cell Therapy Plus Chemotherapy and Radiation After Surgery in Treating Patients With Colorectal Cancer</td>
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**Summary of Evidence**

The evidence for adoptive immunotherapy in patients who have various types of cancer includes randomized controlled trials (RCTs) for many of the cancers, nonrandomized comparative studies, and uncontrolled trials. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. Clinical studies using adoptive immunotherapy are primarily small, early-stage investigations for a variety of cancers. The available RCTs are from non-U.S.
centers in heterogeneous patient populations and interventions, and have methodologic shortcomings that limit conclusions. Studies of cytotoxic T lymphocytes, lymphokine-activated killer cells, tumor-infiltrating lymphocytes, autologous dendritic cells, and genetically engineered T cells suggest that some adoptive immunotherapies may improve outcomes in some cancer types. However, the impact of adoptive immunotherapy on patient outcomes (e.g., increased survival, improved quality of life) has yet to be clarified in large RCTs. Specifically, high-quality RCTs with adequate follow-up are needed to show that there is a significant survival advantage for adoptive immunotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
Current clinical practice guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder, central nervous system, head and neck, hepatobiliary system, kidney, pancreas, stomach, thyroid, melanoma, Hodgkin or non-Hodgkin lymphomas, or non-small-cell lung cancer.

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

Medicare National Coverage
There is no national coverage determination (NCD).

V. DEFINITIONS

**CYTOKINE** is one of more than one hundred distinct proteins produced primarily by white blood cells. They provide signals to regulate immunological aspects of cell growth and function during both inflammation and specific immune response. Each cytokine is secreted by a specific cell in response to a specific stimulus.

**INTERLEUKIN-2** is a cytokine produced by lymphocytes from the tumor itself and is a growth and activation factor for both T-cells and natural killer cells.

**LYMPHOCYTE** is a white blood cell responsible for much of the body’s immune protection.

**NATURAL KILLER CELL (NK)** is a large granular lymphocyte that bonds to cells and lyses them by releasing cytotoxins. NK cells destroy cells infected with viruses and some types of tumor cells in cultures.

**T-CELL** is a lymphoid cell from the bone marrow that migrates to the thymus gland, where it develops into a mature differentiated lymphocyte that circulates between the blood and the lymph, serving as one of the primary cells in the immune response.
VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered when used to report adoptive immunotherapy:

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<td>Adoptive immunotherapy, i.e., development of specific antitumor reactivity (e.g., tumor infiltrating lymphocyte therapy) per course of treatment</td>
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IX. REFERENCES


X. POLICY HISTORY

<table>
<thead>
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<td>MP-4.017</td>
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<td>CAC 1/26/10 – Annual Review</td>
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<td>CAC 5/25/10 – Adopted BCBSA Criteria</td>
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<td>CAC 4/26/11 Consensus</td>
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<td>10/14/11 Added FEP variation to refer to FEP medical policy manual MP-8.01.01, Adoptive Immunotherapy.</td>
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<td>CAC 8/28/12. Consensus review; no changes to policy statements, references updated. Codes reviewed 8/14/12</td>
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<td>05/15/2013- Administrative code review completed.</td>
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<td>CAC 7/30/2013 Consensus review. References updated; rationale added.</td>
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<td>CAC 3/25/14 Consensus review. References updated; rationale added. The wording of the policy statement under adoptive cellular therapy was changed to include CIK cells; however, the intent of both policy statements (i.e., investigational) is unchanged.</td>
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<td>Admin Update 11/9/16: Variation Reformatting</td>
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<td>CAC 1/31/17 Consensus review. Added “autologous” to clarify antigen-loaded dendritic cells. Cross Reference, Rationale and Reference sections updated. Coding reviewed.</td>
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<td>ADOPTIVE IMMUNOTHERAPY</td>
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