MEDICAL POLICY

POLICY TITLE	ADOPTIVE IMMUNOTHERAPY
POLICY NUMBER	MP-4.017

Original Issue Date (Created):	**July 1, 2002**
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Effective Date:	**June 1, 2014**

I. POLICY

Adoptive immunotherapy, using adoptive cellular therapy (ACT) for the administration of cytokine-induced killer (CIK) cells, lymphokine-activated killer cells (LAK) tumor-infiltrating lymphocytes (TIL), or antigen-loaded dendritic cells (ADCs) 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.

Cross-reference
NOTE: Donor leukocyte infusion, used to treat leukemia recurrences in patients who have undergone an allogeneic transplant, is another form of adoptive immunotherapy addressed in a separate policy:

MP-2.004 Donor Leukocyte Infusion for Hematologic Malignancies that Relapse after Allogeneic Stem Cell Transplant
MP-2.039 Tumor Vaccines
MP- 2.151 Cellular Immunotherapy for Prostate Cancer

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II. PRODUCT VARIATIONS

TOP

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

*Refer to FEP Medical Policy Manual MP-8.01.01, Adoptive Immunotherapy. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

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Adoptive immunotherapy is a method of activating lymphocytes for the treatment of cancer and other diseases. It involves the removal of lymphocytes from a patient with cancer, modification of the lymphocytes to increase their reactivity to the cancer, and transfer of the cells back into the patient to treat the cancer. Both non-specific and specific lymphocyte activation are used therapeutically. Non-specific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy (ALT), increases the number of activated lymphocytes. Initially, this was done by harvesting peripheral lymphokine-activated killer (LAK) cells and activating them in vitro with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques yield select populations of 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, tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator.

The spontaneous regression of certain cancers, such as renal cell cancer or melanoma, supports the idea that a patient's immune system can delay tumor progression and, on rare occasions, can eliminate the tumor altogether. These observations led to research interest in a variety of immunologic therapies designed to stimulate a patient's own immune system. The major research challenge in adoptive immunotherapy is to develop immune cells with anti-tumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, two 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." (1) 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 utilizes 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 transfused back 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.

In an attempt to further regulate the host immune system, recent protocols utilize 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 the lymphocytes to the tumor-bearing host.

IV. RATIONALE

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Systematic Reviews

Two systematic reviews have been published on adoptive immunotherapy for postoperative hepatocellular carcinoma. (3, 4) Xie and colleagues performed a meta-analysis of randomized controlled trials (RCTs) comparing adoptive immunotherapy with no adjuvant treatment in patients with hepatocellular carcinoma who had undergone curative resection. (3) Six RCTs (published between 1995 and 2009) including 494 patients met the selection criteria. All 6 trials were conducted in Asia (4 in China, and 2 in Japan) with 2 studies published in the Chinese language. Two trials used cytokine-induced killer cells (CIK) as adoptive immunotherapy, one used CIK plus interleukin-2 (IL-2), and the remaining 3 used LAK plus IL-2. The outcome measures were 1- and 3-year recurrence and survival rates. The overall analysis revealed a significantly reduced risk of both 1-year recurrence (odds ratio [OR]: 0.35; 95% confidence interval [CI]: 0.17-0.71; p=0.003), and of 3-year recurrence (OR: 0.31; 95% CI: 0.16-0.61; 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: 0.45-1.84; 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 the low-to-moderate methodologic quality of the included trials. (3)

Zhong and colleagues also performed a systematic review of RCTs published to May 2011 to evaluate the clinical efficacy of adjuvant adoptive immunotherapy for post-operative patients with hepatocellular carcinoma. (4) Four RCTs (published between 1995 and 2009) including 423 patients met the eligibility criteria. As with the Xie meta-analysis above, (3) all 4 trials were conducted in Asia. Three (of 4) trials in this review were also included in the Xie meta-analysis. The primary outcomes evaluated in this review were OS rate, disease-free survival, and recurrence rates. The secondary outcome was the adverse effects of treatment/toxicity. Owing to the clinical heterogeneity (including operation methods, dose, and type of cytokines) among studies, meta-analysis was not performed. All RCTs reported significantly improved disease-free survival rate or reduced recurrence rate after treatment with adjuvant adoptive immunotherapy ($p<0.05$). However, no statistically significant differences were observed in OS between the 2 study groups across the 3 studies reporting this outcome. The main adverse effect of adoptive immunotherapy was fever (persistent or transient), reported in 3 (of 4) trials. The conclusions of this systematic review (4) are subject to similar limitations as with the above meta-analysis by Xie and colleagues.

Cytokine-induced killer (CIK) cells

Li and colleagues conducted an RCT to evaluate the efficacy of autologous CIK transfusion used in combination with gemcitabine and cisplatin (GC) chemotherapy to treat nasopharyngeal carcinoma in patients with distant metastasis after radiotherapy. (5) From September 2007 to August 2008, 60 patients with distant metastasis after radiotherapy were followed up in a university cancer center in China. The study patients were randomly divided into 2 groups (30 patients in the GC+CIK group were treated with adoptive autologous CIK cell transfusion in combination with GC chemotherapy; 30 patients in the GC group were treated with chemotherapy alone). For the GC+CIK group, the 1- and 2-year OS rates were 90.0% (27/30) and 70% (21/30), respectively, and for the GC group, they were 83.3% (25/30) and 50% (15/30), respectively. The median progression-free survival (PFS) rates were 26 months for the GC+CIK group and 19 months for the GC group. Average survival time was close to 32 months for the GC+CIK group and 26 months for the GC group. Kaplan-Meier survival analysis showed that the OS of the GC+CIK group was higher than that of the GC group, but the difference was not significant ($p=0.1374$, log-rank test). However, the PFS of the GC+CIK group was significantly higher than that of the GC group ($p=0.0234$, log-rank test). The findings of this small single-center RCT indicate that the combination of CIK cells and GC regimen chemotherapy may be a viable treatment option for patients with advanced nasopharyngeal carcinoma. (5)

Liu and colleagues conducted a prospective 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. (6) 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 (IFN)-alpha-2a (arm 2, n=74). The primary endpoint was OS and secondary endpoint was PFS evaluated by Kaplan–Meier analyses and treatment hazard ratios (HRs) with the Cox proportional hazards model. The 3-year PFS and OS in arm 1 were 18% and 61%, as compared with 12% and 23% in arm 2 (p=0.031 and <0.001, all respectively). The 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: 0.84-0.93; p<0.001) and OS (HR: 0.58; 95% CI: 0.48–0.69; p<0.001) in arm 1. These findings suggest that CIK cell immunotherapy has the potential to improve the prognosis of metastatic renal cell carcinoma, and increased frequency of this immunotherapy could result in additional benefits. (6)

Conclusions. Several RCTs from Asia have evaluated the efficacy of CIK in different cancer types. These studies have generally reported some benefits in recurrence rates and/or disease-free survival, however, there has not been a definite benefit reported in OS. This body of evidence is limited by the context of the studies (non-U.S.), the small sample sizes, the heterogeneity of treatment groups, and by other methodologic weaknesses. This evidence is insufficient to determine whether use of CIK in any specific cancer type leads to health outcome benefits.

Lymphokine-activated killer cells (LAK)

Khammari and colleagues studied tumor-specific T cells derived from peripheral blood in a Phase II trial. (7) Lymphocytes were harvested from 14 melanoma patients with regional or distant metastases. The cells were propagated with Melan-A/MART-1, the antigen most commonly expressed by melanoma tumors, and then reinfused with IL-2 and interferon-α (IFN-α). Six patients (43%) experienced an objective response: 2 patients with regional metastases had complete responses, one lasting 20 months and the other lasting more than 60 months; 4 patients with regional metastases had partial responses; and one patient with distant metastases had a partial response. Significant toxicities of treatment included asthenia, flu-like syndrome, and lymphopenia, which were attributed mainly to treatment with interleukin-2 (IL-2) and IFN-α.

Chang and colleagues reported on the results of another Phase II trial in patients with stage IV renal cell cancer who received irradiated autologous tumor cells admixed with Calmette-Guérin bacillus. (8) Seven days later, vaccine-primed lymph nodes were harvested, and the lymphoid cells secondarily activated and then infused back into the patient. Of the 39 patients who participated in the trial, there were 4 complete responses and 5 partial responses.

Kobari and colleagues described the use of intraportal injections of lymphokine-activated killer cells after tumor resection in 12 patients with advanced pancreatic cancer and compared their outcomes to a group of 17 patients who did not receive LAK cells post-resection. (9) The overall survival between the 2 groups was not different.

LAK cells have also been investigated as a treatment of malignant glioma and bladder cancer, but no controlled trials have been published. (10-12)

Takayama and colleagues conducted a study that randomized 150 patients who had undergone a curative resection for hepatocellular carcinoma to receive either adjuvant adoptive immunotherapy or no additional treatment. (13) The immunotherapy consisted of 5 injections over 24 weeks of autologous T cells, harvested from the peripheral blood and cultured for 2 weeks with IL-2. The immunotherapy group had significantly longer recurrence-free survival and disease-specific survival, but overall survival, the final health outcome, did not differ significantly between the 2 groups.

A 1993 randomized trial of lymphokine-activated killer (LAK) cell therapy in patients with metastatic renal cell cancer or melanoma unresponsive to standard therapy failed to show that the use of LAK cells provided any health benefit beyond that associated with IL-2 alone. (14) A 2007 post-hoc analysis of this study found survival benefit in stage III melanoma with one tumor-invaded lymph node; however, this study has not been reproduced.

Conclusions. There is limited evidence on the use of LAK cells for adoptive immunotherapy. Small RCTs have reported benefit on some outcomes, but not on others, and a survival benefit has not been demonstrated. This body of evidence is insufficient to determine whether LAK cells improve outcomes for any specific cancer type.

Tumor-infiltrating lymphocytes (TIL)

Rosenberg and colleagues investigated the ability of adoptive cell transfer utilizing autologous TIL to mediate durable complete regressions in heavily pretreated patients with metastatic melanoma. (15) Ninety-three patients with metastatic melanoma, in 3 clinical trials, were treated with the adoptive transfer of autologous TILs administered in conjunction with IL-2 following a lymphodepleting preparative regimen (chemotherapy with or without radiation). Ninety-five percent of the patients had progressive disease following a prior systemic treatment. Median follow-up was 62 months. Objective response rates by Response Evaluation Criteria in Solid Tumors (RECIST) in the 3 trials were 49%, 52%, and 72%, respectively. Twenty of the 93 patients (22%) achieved complete tumor regression, and 19 have ongoing complete regressions beyond 3 years. Actuarial 3- and 5-year survival rates for the entire group were 36% and 29%, respectively, but for the 20 complete responders were 100% and 93%. The likelihood of achieving a complete response was similar regardless of prior therapy.

Dudley and colleagues (16) conducted a series of Phase II trials examining the administration of TIL and IL-2 to patients with metastatic melanoma under various conditions of pre-infusion lymphodepletion. A nonmyeloablative 7-day chemotherapy regimen (n=43) was compared to ablative regimens of 5-day chemotherapy plus either 200 cGy (n=25) or 1,200 cGy (n=25) total body irradiation. Objective response rates 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; the 10 patients who achieved a complete response had no relapse at a median follow-up of 31 months. Toxicities of treatment occurred primarily in the 1,200 cGy group and included a delay in marrow recovery of 1- to 2-days compared to the other treatment groups, intubation for somnolence, renal insufficiency, and posterior uveitis.

Dreno and colleagues reported on the results of a trial that randomized 88 patients with malignant melanoma without detectable metastases to receive TIL and IL-2 versus IL-2 alone. (17) There was no significant difference in the duration of the relapse-free interval or overall survival. Figlin and colleagues reported the results of a study that randomized 178 patients with metastatic renal cell cancer and resectable renal tumors to receive adjunctive continuous low-dose IL-2 therapy, with or without additional TIL. (18) The TILs were harvested from the surgical specimens. The outcomes were similar in both groups, and for this reason the study was terminated early.

Dendritic cells

Antigen-loaded dendritic cells (ADC) have been explored primarily through early-stage trials in various malignancies including lymphoma, (19) myeloma, (20, 21) subcutaneous tumors, (22) melanoma, (23) non-small cell lung cancer, (24) renal cell cancer, (25) and uterine cervical cancer, (26). A 2012 review article highlights recent progress on dendritic cell-based immunotherapy in epithelial ovarian cancer. (27)

Shi and colleagues conducted a randomized study within a university cancer center in China to evaluate the role of dendritic cell (DC)/CIK combination immunotherapy as maintenance treatment of advanced non-small cell lung cancer. (24) From October 2008 to June 2010, 60 patients with stage IIIB and 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 and CIK cell therapy (n=30), and the other was taken as a control group with no adoptive immunotherapy (n=30). The outcome measures were PFS and the adverse effects of treatment/toxicity. PFS was reported to be prolonged in the DC/CIK group (3.20 months; 95% CI: 2.94-3.50) compared to the control group (2.56 months; 95% CI: 2.39-2.73; $p<0.05$). 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 non-small cell lung cancer. (24)

Ten patients with metastatic medullary thyroid cancer (MTC) were enrolled in a Phase I pilot study (28) and treated with ADCs pulsed with allogeneic MTC tumor cell lysate. After a 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 (HLA) match between patients and tumor cell lines did not predict disease stabilization or progression, suggesting that, should future studies demonstrate

efficacy of ADC therapy of MTC using allogeneic tumor lysate, an unlimited source of tumor material would be available for lysate preparation.

A Phase I study of 5 patients with inoperable pancreatic cancer reinfused ADCs and lymphokine-activated killer (LAK) cells with gemcitabine; antigen priming of the ADCs was presumed to occur in vivo from apoptosis of gemcitabine-exposed tumor cells. (29) 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.

T-cell receptor (TCR) gene therapy

Engineered T cell-based anti-tumor immunotherapy uses tumor-antigen-specific T-cell receptor gene transfer. The 2011 review articles highlight recent progress in this field for solid and hematologic malignancies. (30, 31)

In Phase II trials, Johnson et al. transfected autologous peripheral lymphocytes of 36 metastatic melanoma patients with genes encoding TCRs highly reactive to melanoma/melanocyte antigens (MART-1:27-35 and gp100:154-162). (32) 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, and 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, the eye, and the inner ear. This suggests that ideal targets for TCR gene therapy may be antigens that arise in cancers of nonessential organs (e.g., prostate, ovary, breast, and thyroid) or are not expressed on normal adult tissues (e.g., cancer-testes antigens).

Additional studies have examined TCR gene therapy in Hodgkin (33) and non-Hodgkin lymphoma, (34) prostate tumors, (35) and neuroblastoma. (36)

National Cancer Institute (NCI) Clinical Trial Database

A Phase 3, open, multicentric active trial will randomize patients with stage 3 melanoma to no treatment or treatment with tumor infiltrating lymphocytes combined with IL-2. (NCT00200577) The recruitment status of this trial is unknown because the information has not been verified since February 2010.

Summary

Clinical studies using adoptive immunotherapy are primarily small, early-stage investigations of novel immunologic treatments for a variety of cancers. While there is some evidence that reports a benefit for use of CIK cells on endpoints such as recurrence rates, an improvement in overall survival has not been demonstrated. In addition, the available studies are from non-U.S. centers

in heterogenous patient populations, and have methodologic limitations that limit conclusions. The impact on patient outcomes (e.g., increased survival, improved quality of life) has yet to be clarified in large, randomized, controlled clinical trials. Specifically, high-quality trials with adequate follow-up are needed to show that there is an advantage for the adoptive immunotherapy strategy in important endpoints for a significant cohort of cancer patients compared with standard treatments. Therefore, adoptive immunotherapy remains investigational.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network's (NCCN) Clinical Practice Guidelines in Oncology for melanoma (v 2.2012) address melanoma vaccine but not the types of adoptive immunotherapy addressed in this policy. NCCN guidelines do not address adoptive immunotherapy for kidney cancer (v 1.2012). (37)

V. DEFINITIONS

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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

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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

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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

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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 when used to report Adoptive Immunotherapy:

CPT Codes®								
36511	37799	96365						

HCPCS Code	Description
S2107	Adoptive immunotherapy, ie, development of specific antitumor reactivity (eg, tumor infiltrating lymphocyte therapy) per course of treatment

Investigational for all Diagnosis

*ICD-9-CM Diagnosis Code**	*Description*

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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X. POLICY HISTORY

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MP-4.017	**CAC 7/29/03**
	CAC 5/31/05
	CAC 4/25/06
	CAC 3/27/07
	CAC 1/27/09 Consensus
	CAC 1/26/10 – Annual Review
	CAC 5/25/10 – Adopted BCBSA Criteria
	CAC 4/26/11 Consensus
	10/14/11 Added FEP variation to refer to FEP medical policy manual MP-8.01.01, Adoptive Immunotherapy.
	CAC 8/28/12. Consensus review; no changes to policy statements, references updated. Codes reviewed 8/14/12 klr
	05/15/2013- Administrative code review completed.
	CAC 7/30/2013 Consensus review. References updated; rationale added.
	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 (ie, investigational) is unchanged.

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