MASSACHUSETTS

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Medical Policy
# Adoptive Immunotherapy

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## Policy Number: 455

BCBSA Reference Number: 8.01.01 (For Plans internal use only)
NCD/LCD: N/A

## Related Policies

- Cellular Immunotherapy for Prostate Cancer, #268
- Chimeric Antigen Receptor Therapy for Hematologic Malignancies, #066
- CAR T-Cell Therapy Services for Diffuse Large B-cell Lymphoma (axicabtagene cilleucel or tisagenlecleucel) Prior Authorization Request Form, #924
- CAR T-Cell Therapy Services for B-cell Acute Lymphoblastic Leukemia (tisagenlecleucel) Prior Authorization Request Form, #925
- CAR T-Cell Therapy Services for Mantle Cell Lymphoma (brexucabtagene Autoleucel) Prior Authorization Request Form, #940

## Policy

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Adoptive immunity in the form of chimeric antigen receptor T-cell therapy (eg, tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel) for hematologic malignancies is discussed in policy #066, Antigen Receptor Therapy for Hematologic Malignancies.

All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered **INVESTIGATIONAL** for the indications included, but not limited to, cancers associated with EBV, CMV, nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, NSCLC, melanoma, glioblastoma multiforme, medullary thyroid cancer, pancreatic cancer, and cancers treated with autologous peripheral T lymphocytes containing tumor antigen-specific T cell receptors.

## Prior Authorization Information

**Inpatient**

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|---|---|
| **Commercial Managed Care (HMO and POS)** | This is **not** a covered service. |
| **Commercial PPO and Indemnity** | This is **not** a covered service. |
| **Medicare HMO Blue℠** | This is **not** a covered service. |
| **Medicare PPO Blue℠** | This is **not** a covered service. |

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The following HCPCS code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

### HCPCS Codes

| HCPCS codes: | Code Description |
|---|---|
| S2107 | Adoptive immunotherapy, i.e., development of specific anti-tumor reactivity (e.g., tumor infiltrating lymphocyte therapy) per course of treatment |

## Description

**Adoptive Immunotherapy**

Adoptive immunotherapy uses "activated" lymphocytes as a treatment modality. Both nonspecific and specific lymphocyte activation are used therapeutically. The nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes.

**T Lymphocytes and Killer Cells**

Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them in vitro with the T-cell growth factor interleukin (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 (DC) 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. The 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,]

**Cellular Therapy and Dendritic Cell Infusions**

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 and antigen-loaded DC infusions.

Adoptive cellular therapy is “the administration of a patient’s own (autologous) or donor (allogeneic) antitumor lymphocytes following a lymphodepleting preparative regimen.”[2,] Protocols vary, but include these common steps:

- lymphocyte harvesting (either from peripheral blood or from tumor biopsy)
- propagation of tumor-specific lymphocytes in vitro using various immune modulators
- selection of lymphocytes with reactivity to tumor antigens with enzyme-linked immunosorbent assay
- lymphodepletion of the host with immunosuppressive agents
- adoptive transfer (ie, transfusion) of lymphocytes back into the tumor-bearing host.

Dendritic cell-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. Autologous dendritic cells 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 re-transfused into the patient, where they present antigen to effector lymphocytes (CD4-positive T-cells, CD8-positive 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 policy #268 for a discussion of DC-based immunotherapy for prostate cancer.)

In an attempt to regulate the host immune system further, recent protocols have used various cytokines (eg, 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.

## Summary

The spontaneous regression of certain cancers (eg, renal cell carcinoma, melanoma) supports the idea that a patient’s immune system can delay tumor progression and, on rare occasions, can eliminate tumors altogether. These observations have led to research into various immunologic therapies designed to stimulate a patient’s own immune system. Adoptive immunotherapy is a method of activating lymphocytes and/or other types of cells for the treatment of cancer and other diseases. Cells are removed from the patient, processed for some period of time, and then infused back into the patient.

Allogeneic cell transplantation following nonmyeloablative conditioning of the recipient (known as reduced-intensity conditioning) also may be referred to as “adoptive immunotherapy” in the literature. However, reduced-intensity conditioning 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 reduced-intensity conditioning in cell transplantation is discussed for specific cancers in individual policies related to cell transplantation.

Chimeric antigen receptor T-cell therapies for certain hematologic malignancies (eg, tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel) are discussed separately in policy #066.

**Cytotoxic T Lymphocytes**

For individuals with Epstein-Barr virus-associated cancers who receive cytotoxic T lymphocytes (CTL), the evidence includes 2 small, prospective, noncomparative cohort studies. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), quality of life (QOL), and treatment-related mortality and morbidity. The cohort studies have shown a treatment response to infused CTL directed against cancer-associated viral antigens. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with *Cytomegalovirus*-associated cancers who receive CTL, the evidence includes a single case series. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. In the absence of a randomized controlled trial (RCT) comparing CTL with the standard of care, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Cytotoxic-Induced Killer Cells**

For individuals with nasopharyngeal carcinoma who receive cytotoxic-induced killer (CIK) cells, the evidence includes single RCT. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on progression-free survival (PFS) and OS. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with renal cell carcinoma who receive CIK cells, the evidence includes multiple RCTs. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in PFS and OS with CIK cell-based immunotherapy compared with interleukin (IL)-2 plus interferon-α-2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other 2 RCTs have also reported response rates in favor of CIK therapy with an inconsistent effect on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with gastric cancer who receive CIK cells, the evidence includes 2 meta-analyses encompassing non-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Both meta-analyses reported statistically significant effects on OS, disease-free survival (DFS), and PFS in favor of immunotherapy versus no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with colorectal cancer who receive CIK cells, the evidence includes a single RCT and 1 meta-analysis. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on OS in favor of immunotherapy versus chemotherapy alone. A meta-analysis that included both gastric cancer and colorectal cancer found improvements in OS and PFS in favor of CIK/dendritic cells (DC)-CIK compared to chemotherapy alone. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hepatocellular carcinoma who receive CIK cells, the evidence includes meta-analyses that include RCTs and quasi-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Meta-analyses of these trials have reported improved OS rates when compared to conventional therapies alone, but they are limited by inclusion of studies from Asia only and heterogeneity in comparators. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate

randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-small-cell lung cancer who receive CIK cells, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A single systematic review of RCTs reported some benefits in median time to progression and median survival time. The trials assessed in the systematic review were limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Tumor-Infiltrating Lymphocytes**
For individuals with melanoma who receive tumor-infiltrating lymphocytes (TILs), the evidence includes a meta-analysis of randomized and non-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A meta-analysis evaluating TIL with IL-2 in patients with cutaneous melanoma reported an objective response rate of 41%. Pooled 1-year OS rates ranged from 46.1% to 56.5% depending on the IL-2 dose level. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Dendritic Cells**
For individuals with glioblastoma multiforme who receive DC, the evidence includes a systematic review of observational studies. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Because of the observational and noncomparative nature of the available evidence, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. Interim results from 1 such RCT have been published but are not informative because the patients were unblinded and results combined for the treatment and placebo arms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-small-cell lung cancer who receive DC, the evidence includes 2 RCTs and a meta-analysis. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCTs have generally reported some benefits in response rates and/or survival. The meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. Most trials were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with medullary thyroid cancer who receive DC, the evidence includes 1 prospective noncomparative study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A small prospective noncomparative study in 10 medullary thyroid cancer patients treated with autologous DC has been published. There are no RCTs comparing DC-based adoptive immunotherapy with the standard of care and, therefore, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm

showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pancreatic cancer who receive DC, the evidence includes a small prospective noncomparative study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The study reported on treatment outcomes for 5 patients with pancreatic cancer. Because of the noncomparative nature of the available evidence and small sample base, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Genetically Engineered T Cells**

*Peripheral T Lymphocytes*

For individuals with cancers who receive autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors, the evidence includes multiple small observational studies. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Multiple observational studies have examined autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors in melanoma, Hodgkin and non-Hodgkin lymphoma, prostate tumors, and neuroblastoma. Because of the noncomparative nature of the available evidence and small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## Policy History

| Date | Action |
|---|---|
| 12/2021 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 12/2020 | Annual policy review. Policy section clarified to: All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered investigational for the indications included, but not limited to, in this policy. |
| 12/2019 | Annual policy review. Sections regarding use of tisagenlecleucel and axicabtagene ciloleucel were removed and added to new policy #066 Chimeric Antigen Receptor Therapy for Hematologic Malignancies), references updated. Policy section clarified to 'All applications of adoptive immunotherapy evaluated in this policy are considered investigational.' Clarified coding information. |
| 3/2019 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 1/2019 | Clarified coding information. |
| 5/2016 | Annual policy review. Section on lymphokine-activated killer cell deleted due to obsolete intervention. Effective 5/1/2016. |
| 5/2015 | Annual policy review. Clarified coding information. New investigational indications described. Effective 5/1/2015. |
| 3/2014 | New references added from BCBSA National medical policy. |
| 6/2013 | The wording of the policy statement under adoptive cellular therapy was changed to include cytokine-induced killer (CIK) cells; however, the intent of both policy statements (i.e., investigational) is unchanged. Effective 6/1/2013. |
| 11/2011-4/2012 | Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements. |
| 1/17/2012 | Annual policy review. No changes to policy statements. |

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|---|---|
| 1/1/2012 | Updated removing information on donor leukocyte infusion which is now addressed in medical policy #338. |
| 7/2011 | Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements. |
| 9/2010 | Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements. |
| 4/2010 | Annual policy review. No changes to policy statements. |
| 9/2009 | Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements. |
| 9/2009 | Annual policy review. Changes to policy statements. |
| 2/2009 | Annual policy review. No changes to policy statements. |
| 10/2008 | Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements. |
| 9/2008 | Annual policy review. No changes to policy statements |
| 11/2007 | Annual policy review. No changes to policy statements. |
| 9/2007 | Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements. |
| 8/2007 | Annual policy review. No changes to policy statements. |

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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