8.01.53	Cellular Immunotherapy for Prostate Cancer		
Original Policy Date:	January 7, 2011	**Effective Date:**	September 1, 2023
Section:	8.0 Therapy	**Page:**	Page 1 of 12

Policy Statement

I. Sipuleucel-T therapy may be considered **medically necessary** in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer.

II. Sipuleucel-T therapy is considered **investigational** for the treatment of prostate cancer in all other situations, including but not limited to:
   A. Treatment of hormone-responsive prostate cancer
   B. Treatment of moderate-to-severe symptomatic metastatic prostate cancer
   C. Treatment of visceral (liver, lung, or brain) metastases

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

Policy Guidelines

Coding

The following HCPCS code is available for this product:

- **Q2043**: Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion

Description

Sipuleucel-T (Provenge) is a class of therapeutic agent used to treat asymptomatic-or minimally symptomatic-castration-resistant, metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and reinfused into the patient. The proposed mechanism of action is that treatment stimulates the patient's own immune system to resist cancer spread.

Related Policies

- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2010, the U.S. Food and Drug Administration approved Provenge® (sipuleucel-T; Dendreon Corp, now Sanpower) under a biologics licensing application for "the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer."4, Approval was contingent on the manufacturer conducting a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 men with prostate cancer who receive sipuleucel-T.

Rationale

Background

Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths among American men, with an estimated incidence of 164690 cases and an estimated number of 29430 deaths in 2018.[1,] In most cases, prostate cancer is diagnosed at a localized stage and is treated with prostatectomy or radiotherapy. However, some patients are diagnosed with metastatic or recurrent disease after treatment of localized disease.

Treatment

Androgen ablation is the standard treatment for metastatic or recurrent disease. Most patients who survive long enough eventually develop androgen-independent (castration-resistant) prostate cancer. At this stage of metastatic disease, docetaxel, a chemotherapeutic agent, has demonstrated a survival benefit of 1.9 to 2.4 months in randomized clinical trials.[2,3,] Chemotherapy with docetaxel causes adverse events in large proportions of patients, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms. Trials evaluating docetaxel included both asymptomatic and symptomatic patients, and results have suggested a survival benefit for both groups. Because of the burden of treatment and its adverse events, most patients defer docetaxel treatment until cancer recurrence is symptomatic.

Cancer immunotherapy has been investigated as a treatment that could be instituted at the point of detection of androgen-independent metastatic disease before significant symptomatic manifestations have occurred. The quantity of cancer cells in the patient during this time is thought to be relatively low, and it is thought that an effective immune response to cancer during this interval could effectively delay or prevent progression. Such a delay could allow a course of effective chemotherapy, such as docetaxel, to be deferred or delayed until necessary, thus providing an overall survival benefit.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in

some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

Metastatic, Castration-Resistant Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of cellular immunotherapy with sipuleucel-T (Provenge) in individulas who have metastatic castration-resistant prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals who have asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.

Interventions

The therapy being considered is cellular immunotherapy, specifically, sipuleucel-T (Provenge), a newer class of therapeutic agent used to treat asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and reinfused into the patient. The cells are administered as 3 intravenous infusions given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient's own immune system to resist cancer spread.

Comparators

The following therapy is currently being used to make decisions about asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer: standard treatment includes docetaxel, a chemotherapeutic agent. Chemotherapy with docetaxel causes adverse events in large proportions of patients, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms.

Outcomes

The general outcomes of interest are the time to progression, mortality, and toxicity from treatment. Median survival for metastatic castration-resistant prostate cancer is less than 2 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Yi et al (2016) reported on a meta-analysis that identified 3 RCTs on sipuleucel-T for treating castration-resistant prostate cancer (see details below).[5] A pooled analysis of the 3 RCTs found significantly improved overall survival (OS) with sipuleucel-T compared with placebo (hazard ratio [HR], 0.73 ; 95% confidence interval [CI], 0.61 to 0.88; I^2=0%). There was no significant difference between sipuleucel-T and placebo in time to progression of prostate cancer (HR , 0.88; 95% CI, 0.74 to 1.06; I^2=4%). Rates of individual adverse events were pooled, and there were no significant differences between sipuleucel-T and placebo in any of the adverse events, which consisted of fatigue, back pain, headache, arthralgia, and constipation. Stroke rates were not reported.

Randomized Controlled Trials

Sipuleucel-T has been studied in 3 double-blind, placebo-controlled randomized trials.[6] These trials were published by Small et al (2006),[7] Higano et al (2009),[8] and Kantoff et al (2010),[9] and were reviewed by the U.S. Food and Drug Administration (FDA).[10] Patients enrolled in these trials all had castration-resistant metastatic prostate cancer, were asymptomatic or mildly symptomatic, in good physical health characterized by the Eastern Cooperative Oncology Group Performance Status at 0 or 1, and had tumors with positive staining for prostatic acid phosphatase.

Table 1 describes the 2 early identically designed studies.[6,7,8,10] Patients with asymptomatic metastatic prostate cancer were randomized to sipuleucel-T or to a control infusion of untreated dendritic cells. The principal outcome was time to disease progression, defined as the time from randomization to the first observation of disease progression. Disease progression could be defined as radiologic progression (based on several imaging criteria), clinical progression (based on prostate cancer-related clinical events [e.g., pathologic fracture]), or pain progression (based on onset of pain corresponding to the anatomic location of the disease).

Studies were not designed to establish efficacy based on OS. On the progression of cancer, patients were allowed additional treatment as needed, including chemotherapy. Patients originally assigned to placebo were allowed to cross over by receiving their own dendritic cells pulsed with PA2024 antigen (recombinant fusion protein comprising human prostatic acid phosphatase linked to granulocyte-macrophage-colony-stimulating factor) but prepared from frozen dendritic cells harvested from their initial leukapheresis procedures.

Table 1. Characteristics of Randomized Phase 3 Trials of Sipuleucel-T

Study	Design	Eligibility	Treatment	Outcomes
9901A[7] **9902A**[8]	Randomized double-blind, placebo-controlled	Metastatic prostate cancer by imaging, asymptomatic and progressing by imaging or rising PSA	3 infusions of vaccine or 3 infusions of placebo dendritic cells	• Primary: disease progression (radiologic, clinical, pain) • Secondary: time to pain, time to progression
IMPACT[9]	Randomized double-blind, placebo-controlled	Metastatic prostate cancer by imaging, asymptomatic or minimally symptomatic and progressing by imaging or rising PSA	3 infusions of vaccine or 3 infusions of placebo dendritic cells	• Primary: overall survival • Secondary: time to objective disease progression

IMPACT: A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy With Autologous Antigen Presenting Cells Loading With PA2024 (Provenge(R), APC8015) in Men With Metastatic Androgen Independent Prostatic Adenocarcinoma; PSA: prostate-specific antigen.

As shown in Table 2, results of study 9901A for the principal outcome of time to progression did not show a significant difference between the vaccine and infusion control. Median time to progression was 11.7 weeks for the vaccine group and 10.0 weeks for the control group.

Table 2. Results of the Randomized, Phase 3 Trials of Sipuleucel-T

Study	Vaccine Group	Control Group	p
Study 9901A[7,]			
n	82	45	
Median time to progression, wk	11.7	10.0	.052
Median time to clinical progression, wk	10.7	9.1	.061
Median overall survival, mo	25.9	21.4	.01
Overall survival at 36 mo, %	34	11	.005 (multivariable adjusted,.002)
Study 9902A[8,]			
n	65	33	
Median time to progression, wk	10.9	9.9	.719
Median overall survival, mo	19.0	15.7	.331
IMPACT study[9,]			
n	341	171	
Overall median survival, mo	25.8	21.7	.032
Overall survival at 36 mo, %	31.7	23.0	.036
Time to progression	Not reported	Not reported	HR, 0.95;.628

HR: hazard ratio; IMPACT: A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy With Autologous Antigen Presenting Cells Loading With PA2024 (Provenge(R), APC8015) in Men With Metastatic Androgen Independent Prostatic Adenocarcinoma.

A survival analysis of study 9901A was presented in the FDA briefing document, with caveats that the study was not powered to show a survival effect and that a primary method of survival analysis was not prespecified in the protocol. Median survival times were 25.9 months for vaccine-treated patients and 21.4 months for placebo-treated patients, a statistically significant difference (p=.011). At 36 months, the survival rate was 34% for vaccine-treated patients and 11% for placebo-treated patients. The FDA briefing document also analyzed possible confounders in the survival analysis.[10,] After disease progression, patients in both groups received chemotherapy; however, the rate of chemotherapy was slightly higher in the placebo group (48% vs. 36%, respectively). Examination of the causes of death did not reveal any obvious spurious elevation of noncancer deaths in the placebo group. The published version of study 9901A by Small et al (2006) analyzed the survival data after adjusting for prognostic factors and found a significant association between sipuleucel-T treatment and survival (HR , 2.12; 95% CI, 1.31 to 3.44).[7,]

Because study 9901A did not meet its principal outcome endpoint for efficacy, enrollment for its partner study 9902A was suspended. Its sample size was, therefore, smaller, and the study subsequently had lower statistical power. As shown in Table 2, results for study 9902A showed a median time to progression of 10.9 weeks in the vaccine group versus 9.9 weeks in the placebo group, which was not statistically significant. A survival analysis of study 9902A showed that median survival was 19 months in vaccine-treated patients and 15.7 months with control, which also was not statistically significant.

Higano et al (2009) pooled survival data from the 2 studies.[8,] Pooled analysis showed a 33% reduction in the risk of death (HR , 1.50; 95% CI, 1.10 to 2.05; p=.011). The association was robust to adjustments in imbalances in baseline prognostic factors and postprogression chemotherapy use. Because these earlier studies did not meet criteria for success for their principal endpoints, the FDA did not approve sipuleucel-T in 2007. A larger phase 3 trial of similar design, Immunotherapy for Prostate Adenocarcinoma Treatment, enrolling 512 patients, was designed with a principal endpoint of OS.[9,] Analyses used to support the FDA approval reported a 22% reduction in overall mortality in patients treated with sipuleucel-T. Treatment extended median survival by 4.1 months compared with placebo (25.8 months vs. 21.7 months, respectively) and improved relative 3-year survival by 38%

compared with placebo (31.7% vs. 23.0%, respectively). Results adjusted for subsequent docetaxel use and timing, as well as analyses examining prostate cancer-specific survival, showed a similar magnitude and statistical significance of the survival benefit. Of note, 14% of enrolled subjects in this trial had received prior docetaxel. In a retrospective, prespecified, multivariate subgroup analysis by Schellhammer et al (2013), several baseline factors were associated with OS: prostate-specific antigen (PSA) levels, lactate dehydrogenase levels, hemoglobin levels, the Eastern Cooperative Oncology Group Performance Status scores, alkaline phosphatase levels, and Gleason scores.[11,] Analysis of PSA levels by quartiles showed that men in the lowest quartile had the greatest survival benefit with sipuleucel-T: 49% reduced mortality rate, compared with 26% reduced mortality rate in the second quartile, 19% in the third quartile, and 16% in the highest quartile.

Small et al (2014) pooled data for time to disease-related pain and time to the first use of opioid analgesics from all 3 RCTs.[12,] Median time to disease-related pain was 5.6 months for sipuleucel-T and 5.3 months for control (HR , 0.82; 95% CI, 0.62 to 1.09). Median time to the first use of opioid analgesics was 12.6 months for sipuleucel-T and 9.7 months for control (HR , 0.76; 95% CI, 0.58 to 0.99).

Regarding the safety of sipuleucel-T, most adverse events were grade 1 and 2 and resolved within 48 hours. The rate of serious adverse events did not differ statistically between vaccine- and placebo-treated patients. However, a difficulty in assessing potential adverse events by comparing sipuleucel-T with placebo is that placebo comprised infusion of untreated dendritic cells, which may cause adverse events. The FDA reviewers expressed concern about a possible association of sipuleucel-T with cerebrovascular events; 8 (5%) of 147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared with zero placebo-treated patients in the 2 early trials.[10,] In the FDA review summarizing cerebrovascular event rates from studies 9901A, 9902A, and interim Immunotherapy for Prostrate Adenocarcinoma Treatment data, the incidence of stroke was 4.9% (17/345) in sipuleucel-T-treated patients and 1.7% (3/172) in placebo-treated patients (p=.092). The FDA review called the cerebrovascular event rate a "potential safety signal" and included as part of its approval a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 patients with prostate cancer who receive sipuleucel-T.

Section Summary: Metastatic, Castration-Resistant Prostate Cancer

For patients with metastatic, castration-resistant prostate cancer, 3 RCTs of sipuleucel-T have been published. The 3 RCTs are consistent in reporting an improvement in OS of approximately 4 months compared with placebo. Additionally, 2 trials also reported that 36-month survival was significantly improved for patients receiving sipuleucel-T, with absolute improvements in survival of 9% and 23%. Time to progression was slightly longer in the sipuleucel-T groups but this difference was not statistically significant. A meta-analysis of the 3 RCTs found significantly improved OS, but not the time to progression, with sipuleucel-T compared with placebo. Serious adverse events were not increased in the sipuleucel-T groups. However, given data reported to the FDA, there was a concern about a possible increase in stroke risk and this is being studied in an ongoing postmarketing study.

Nonmetastatic, Androgen-dependent Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of cellular immunotherapy with sipuleucel-T (Provenge) in individuals who have nonmetastatic, androgen-dependent prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals who have nonmetastatic, androgen-dependent prostate cancer.

Interventions
The therapy being considered is cellular immunotherapy, specifically sipuleucel-T (Provenge), a newer class of therapeutic agent used to treat asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and reinfused into the patient. The cells are administered as 3 intravenous infusions given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient's own immune system to resist cancer spread.

Comparators
The following therapy is currently being used to make decisions about cellular immunotherapy: androgen deprivation therapy is the standard treatment for metastatic or recurrent disease.

Outcomes
The general outcomes of interest are the time to progression, mortality, and toxicity from treatment. The time frame for outcome measures varies from short-term management of toxicity and symptoms of cancer progression or recurrence and OS.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
Beer et al (2011) published an RCT evaluating sipuleucel-T in the setting of nonmetastatic, androgen-dependent prostate cancer.[13,] Patients with prostate cancer detectable by PSA levels after radical prostatectomy received 3 to 4 months of androgen suppression therapy and were then randomized (2:1) to sipuleucel-T (n=117) or to control (n=59). The primary endpoint was time to biochemical failure. The median time to biochemical failure was 18.0 months for sipuleucel-T and 15.4 months for control. The difference between groups was not statistically significant (HR , 0.936 ; p=.737). The PSA doubling time after testosterone recovery was 155 days in the sipuleucel-T group and 105 days in the placebo group (p=.038). At the data cutoff point, 16% developed distant failure. The risk of distant failure did not significantly favor the sipuleucel-T group (p=.021); however, the authors noted that this analysis had limited power.

Section Summary: Nonmetastatic, Androgen-Dependent Prostate Cancer
Only 1 RCT has evaluated sipuleucel-T in patients with nonmetastatic, androgen-dependent prostate cancer. This trial did not show a statistically significant benefit for sipuleucel-T compared with control. Therefore, evidence on the treatment of nonmetastatic prostate cancer is not sufficiently robust to determine that health outcomes are improved.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association

The American Urological Association (2023) authored a guideline on advanced prostate cancer.[14,] There is a conditional recommendation to offer sipuleucel-T to patients with metastatic castration-resistant prostate cancer who are asymptomatic or minimally symptomatic (level of evidence grade B). Sipuleucel-T should not be used in patients with large tumor burdens, visceral disease, rapid progression, or symptomatic disease that requires opioids.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (v.1.2023) guidelines for prostate cancer recommend sipuleucel-T as a category 1 treatment only for patients with metastatic castration-recurrent prostate cancer, asymptomatic or minimally symptomatic; Eastern Cooperative Oncology Group Performance Status 0 or 1; no liver metastasis; and life expectancy greater than 6 months.[15,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2011) released a national coverage determination approving sipuleucel-T for the treatment of asymptomatic or minimally symptomatic castration-resistant prostate cancer.[16,] Coverage for off-label indications was left to the discretion of local Medicare administrative contractors.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05806814[a]	Pilot Trial to Investigate Immune Response to an Extended Course of Sipuleucel-T Immunotherapy in Patients With Metastatic Castration-resistant Prostate Cancer (EXCITE Trial)	12	Feb 2027
NCT05751941	A Phase II Randomized Study of Sipuleucel-T With or Without Continuing New Hormonal Agents (NHA) in Metastatic Prostate Cancer With PSA Progression While on NHA and LHRH Analog	26	Oct 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

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16. Center for Medicare and Medicaid Services. National Coverage Determination (NCD) for Autologous Cellular Immunotherapy Treatment (110.22). 2011; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=344&ncdver=1&bc=AAAAIAAAAAAA&. Accessed May 22, 2023.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Previous treatment and response
  - Severity of current symptoms

- Type and location of cancer (localized or metastatic)
- Hormone (androgen) responsiveness status

Post Service (in addition to the above, please include the following):

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	36511	Therapeutic apheresis; for white blood cells
	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
HCPCS	Q2043	Sipuleucel-T, minimum of 50 million autologous cd54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
04/05/2011	Administrative Review
09/30/2014	Policy revision without position change
02/01/2017	Policy revision without position change
09/01/2017	Policy revision without position change
09/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
10/01/2020	Annual review. No change to policy statement. Literature review updated.
09/01/2021	Annual review. No change to policy statement. Literature review updated.
09/01/2022	Annual review. No change to policy statement. Literature review updated.
09/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished

primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

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

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Cellular Immunotherapy for Prostate Cancer 8.01.53 **Policy Statement:** I. Sipuleucel-T therapy may be considered **medically necessary** in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer. II. Sipuleucel-T therapy is considered **investigational** for the treatment of prostate cancer in all other situations, including but not limited to: A. Treatment of hormone-responsive prostate cancer B. Treatment of moderate-to-severe symptomatic metastatic prostate cancer C. Treatment of visceral (liver, lung, or brain) metastases	**Cellular Immunotherapy for Prostate Cancer 8.01.53** **Policy Statement:** I. Sipuleucel-T therapy may be considered **medically necessary** in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer. II. Sipuleucel-T therapy is considered **investigational** for the treatment of prostate cancer in all other situations, including but not limited to: A. Treatment of hormone-responsive prostate cancer B. Treatment of moderate-to-severe symptomatic metastatic prostate cancer C. Treatment of visceral (liver, lung, or brain) metastases