

## MEDICAL POLICY – 8.01.53

## Cellular Immunotherapy for Prostate Cancer

BCBSA Ref. Policy: 8.01.53

Effective Date: Oct. 1, 2024

Last Revised: Sept. 9, 2024

Replaces: N/A

## RELATED MEDICAL POLICIES:

2.04.514 Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)  
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)



Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Immunotherapy is a way to fight disease, even cancer, by using a person's own immune system. Dendritic cells are part of the immune system. They help the immune system spot cancer cells. When the dendritic cells find and start to break down cancer cells, other immune cells are activated to also attack the cancer cells. In some cases of advanced prostate cancer, a vaccine can be made using a person's own immune cells. Certain immune cells are removed, treated in a lab to create dendritic cells, and then given back to the person. This very specialized vaccine then helps the body fight prostate cancer. This policy describes when this type of immunotherapy may be approved for prostate cancer.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

Therapy	Medical Necessity
<b>Sipuleucel-T therapy</b>	<p><b>Sipuleucel-T therapy may be considered medically necessary in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer.</b></p> <p><b>Note:</b> Provenge is the brand or trade name for sipuleucel-T.</p>

Therapy	Investigational
<b>Sipuleucel-T therapy</b>	<p><b>Sipuleucel-T therapy is considered investigational in all other situations, including but not limited to:</b></p> <ul style="list-style-type: none"> <li>• Treatment of hormone-responsive prostate cancer</li> <li>• Treatment of moderate to severe symptomatic metastatic prostate cancer</li> <li>• Treatment of visceral (liver, lung, or brain) metastases</li> </ul>

Documentation Requirements
<p><b>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include clinical documentation of all of the following:</b></p> <ul style="list-style-type: none"> <li>• Individual has metastatic prostate cancer that is castrate-resistant (does not respond to hormone treatment)</li> <li>• Individual is asymptomatic or minimally symptomatic</li> <li>• Individual has no liver, lung, or brain metastases</li> </ul>

## Coding

Code	Description
<b>HCPCS</b>	
Q2043	Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion (Provenge)

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## Related Information

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N/A

## Evidence Review

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### 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 individual through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and reinfused into the individual. The proposed mechanism of action is that treatment stimulates the individual's own immune system to resist cancer spread.

### Background

#### Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths among American men, with an estimated incidence of 299,010 cases and an estimated 35,250 deaths in 2024.<sup>1</sup> In most cases, prostate cancer is diagnosed at a localized stage and is treated with prostatectomy or radiotherapy. However, some individuals are diagnosed with metastatic disease or recurrent disease after treatment of localized disease.

#### Treatment

Androgen ablation is the standard treatment for metastatic or recurrent disease. Most individuals 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.<sup>2,3</sup>

Chemotherapy with docetaxel causes adverse effects in large proportions of individuals, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms. Trials evaluating docetaxel included both asymptomatic and symptomatic individuals, and results have suggested a survival benefit for both groups. Because of the burden of treatment and its adverse effects, most individuals 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 individual during this time is thought to be relatively low, and it is thought that an effective immune response to the 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.

## Summary of Evidence

For individuals who have asymptomatic or minimally symptomatic, metastatic castration-resistant prostate cancer who receive sipuleucel-T (Provenge), the evidence includes three randomized controlled trials (RCTs) and a systematic review of these RCTs. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The two earlier RCTs of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third RCT, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All three studies were consistent in demonstrating that sipuleucel-T does not delay time to measurable progression of disease. A meta-analysis of the three RCTs found significantly improved overall survival, but not time to progression, with sipuleucel-T compared with placebo. Serious adverse events did not increase in the sipuleucel-T group. However, the available data suggested, but did not confirm, an increase in stroke risk; this risk is being evaluated in a post marketing study. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have nonmetastatic androgen-dependent prostate cancer who receive sipuleucel-T (Provenge), the evidence includes an RCT. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT did not find a statistically significant difference between sipuleucel-T and a control in time to biochemical failure. The RCT was not designed to evaluate the impact of sipuleucel-T on mortality. The evidence is insufficient to determine that technology results in an improvement in the net health outcome.



## Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in [Table 1](#).

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<a href="#">NCT06134232</a>	An Open -Label, Multicenter Study of Subjects With Metastatic Castrate-Resistant Prostate Cancer Treated With PROVENGE <sup>®</sup> and Boosted With A Single Infusion of Sipuleucel-T to Measure Immune Response	400	Jun 2032
<a href="#">NCT05806814</a> <sup>a</sup>	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	May 2024
<a href="#">NCT05751941</a>	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.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion 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.<sup>14</sup> There is a conditional recommendation to offer sipuleucel-T to individuals with metastatic castration-resistant prostate cancer who are asymptomatic or minimally symptomatic (level of evidence grade B). Sipuleucel-T should not be used in individuals with large tumor burdens, visceral disease, rapid progression, or symptomatic disease that requires opioids.

## National Comprehensive Cancer Network (NCCN)

Current National Comprehensive Cancer Network (v.3.2024) guidelines for prostate cancer recommend sipuleucel-T as a category 1 treatment only for individuals with metastatic castration-recurrent prostate cancer, symptomatic or minimally symptomatic; Eastern Cooperative Oncology Group Performance Status 0 or 1; no liver metastasis; and life expectancy greater than 6 months.<sup>15</sup> Sipuleucel-T is not recommended for patients with small cell prostate cancer/NEPC. It is an option for patients who have had prior treatment with docetaxel or a novel hormone therapy, but not for those who received both.<sup>15</sup>

## Medicare National Coverage

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

## Regulatory Status

In 2010, the US Food and Drug Administration approved Provenge (sipuleucel-T; Dendreon Corp.) under a Biologics Licensing Application for "the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer."<sup>4</sup> Approval was contingent on the manufacturer conducting a post marketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 men with prostate cancer who receive sipuleucel-T.



## References

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## History

Date	Comments
11/09/10	New Policy; add to Therapy section - New policy.
05/13/11	Code Update - C9273 added to policy.
10/11/11	Replace Policy – Previously unpublished preliminary trial information updated with published information. Medicare coverage decision granted 6/30/2011; section updated. Reference 8 added. No change to the policy statement. Codes updated: HCPCS code C9273 deleted and Q2043 added; ICD-9 codes updated; ICD-10 codes added.
11/17/11	Reviewed and recommended by OAP on November 17, 2011.
10/26/12	Replace Policy. Policy updated with literature review. Reference 10 added. No change to policy statements.
02/15/13	Update Related Policies. Add 8.01.01.
09/27/13	Replace policy. Policy updated with literature review through May 2013. Reference 10 added. No change to policy statements.
09/23/14	Annual Review. Policy updated with literature review through June 20, 2014. References 6, 8, and 12 added; references 3, 7, 10, and 13 updated; others renumbered/removed. Policy statements unchanged. CPT code 96365 removed from policy; this code is not managed in relationship to this policy.
09/08/15	Annual Review. "Hormone-refractory" changed to the current clinically accepted term "castration-resistant" prostate cancer in the medically necessary policy statement and throughout the policy. Added brand name Provenge® to the policy section. Policy updated with literature review through June 27, 2015; references 1, 10, and 14 added. Policy statements wording revised as noted. CPT code 36511 and HCPCS code J3590 removed; these do not relate to the policy.
12/01/16	Annual Review, approved November 8, 2016. No changes to policy statement.
09/01/17	Annual Review, approved August 22, 2017. Policy updated with literature review through June 6, 2017; references 5 and 14-15 added. Policy statement unchanged.
10/01/18	Annual Review, approved September 20, 2018. Policy updated with literature review through June 2018; references 15 and 18 added; reference 1 updated. Policy statements unchanged.
10/10/18	Minor edit, added Documentation Requirements section.
10/01/19	Annual Review, approved September 5, 2019. Policy updated with literature review through May 2019; reference on NCCN updated. Policy statements unchanged.
10/01/20	Annual Review, approved September 17, 2020. Policy updated with literature review through April 2020; no references added. Policy statements unchanged.





Date	Comments
10/01/21	Annual Review, approved September 2, 2021. Policy updated with literature review through April 19, 2021; no references added; NCCN guideline updated. Policy statements unchanged.
09/01/22	Annual Review, approved August 22, 2022. Policy updated with literature review through April 18, 2022; no references added; NCCN guideline updated. Policy statements unchanged.
10/01/23	Annual Review, approved September 11, 2023. Policy updated with literature review through May 15, 2023; reference added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
10/01/24	Annual Review, approved September 9, 2024. Policy updated with literature review through May 17, 2024; no references added. Policy statements unchanged.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

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