Policy Statement

Use of any focal therapy modality to treat patients with localized prostate cancer is considered investigational.

Policy Guidelines

There is no specific CPT code for many of these focal treatments. It is likely they are reported with the following CPT code:

- **55899**: Unlisted procedure, male genital system

The following HCPCS code is specific to this procedure:

- **C9747**: Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance

**Effective January 1, 2020**, the following CPT code describes ultrasound guided transurethral ablation of prostate tissue for treating prostate cancer using thermotherapy with water vapor generated by high energy direct current:

- **0582T**: Transurethral ablation of malignant prostate tissue by high-energy water vapor thermotherapy, including intraoperative imaging and needle guidance

**Effective January 1, 2019**, the following CPT code describes radiofrequency generated water vapor thermotherapy:

- **53854**: Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy

Description

Prostate cancer is the second most common cancer diagnosis men receive in the United States, and the behavior of localized prostate cancer can prove difficult to predict on a case-by-case basis. Most men with the cancer undergo whole-gland treatments, which can often lead to substantial adverse events. To reduce tumor burden and minimize morbidity associated with radical treatment, investigators have developed a therapy known as focal treatment. Focal treatment seeks to ablate either an “index” lesion (defined as the largest cancerous lesion with the highest grade tumor), or alternatively, to ablate nonindex lesions and other areas where cancer has been known to occur. Addressed in this review are several ablative methods used to remove cancerous lesions in localized prostate cancer (e.g., focal laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation, photodynamic therapy). All methods, except focal laser ablation, use ultrasound guidance to focus on the tumor (focal laser ablation uses magnetic resonance imaging to guide the probe).

Related Policies

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Magnetic Resonance-Guided Focused Ultrasound
- Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer
- Whole Gland Cryoablation of Prostate Cancer
Benefit Application

Benefit determinations should be based 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

Focal Laser Ablation
In 2010, the Visualase® Thermal Therapy System (Medtronic) and, in 2015, the TRANBERG Laser fiber (Clinical Laserthermia Systems) were cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under MRI guidance for multiple indications including urology, at wavelengths from 800 to 1064 nm. FDA product code: LLZ, GEX, FRN.

High-Intensity Focused Ultrasound
In October 2015, the Sonablate® 450 (SonaCare Medical) was cleared for marketing through the 510(k) process after approval of a de novo request and classification as class II under the generic name “high intensity ultrasound system for prostate tissue ablation”. This device was the first of its kind to be approved in the United States. In November 2015, Ablatherm®-HIFU (EDAP TMS) was cleared for marketing by the FDA through the 510(k) process.

Cryoablation
Some cryoablation devices cleared for marketing by the FDA through the 510(k) process for cryoablation of the prostate include: Visual-ICE® (Galil Medical), Ice Rod CX, CryoCare® (Galil Medical), IceSphere (Galil Medical), and Cryocare® Systems (Endocare®, HealthTronics). FDA product code: GEH.

Radiofrequency Ablation
Radiofrequency ablation devices have been cleared for marketing by the FDA through the 510(k) process for general use for soft tissue cutting and coagulation and ablation by thermal coagulation. Under this general indication, radiofrequency ablation may be used to ablate tumors. FDA product code: GEI.

Photodynamic Therapy
The FDA has granted approval to several photosensitizing drugs and light applicators. porfimer sodium (Photofrin®; Axcan Pharma) and psoralen are photosensitizer ultraviolet lamps used to treat cancer; they were cleared for marketing by the FDA through the 510(k) process. FDA product code: FTC.

Rationale

Background
Prostate Cancer
Prostate cancer is the second most common cancer diagnosed among men in the United States. According to the National Cancer Institute, nearly 240,000 new cases were diagnosed in the United States in 2013 and would be associated with around 30,000 deaths. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years.¹ However, the National...
Cancer Institute Surveillance Epidemiology and End Results Program data have shown age-adjusted cancer-specific mortality rates for men with prostate cancer declined from 40 per 100,000 in 1992 to 22 per 100,000 in 2010. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

**Diagnosis**
From a clinical standpoint, different types of localized prostate cancers may appear similar during initial diagnosis. However, the cancer often exhibits varying degrees of risk progression that may not be captured by accepted clinical risk categories (e.g., D’Amico criteria) or prognostic tools based on clinical findings (e.g., PSA titers, Gleason grade, or tumor stage). In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15% to 20% to perhaps 27% at 20-year follow-up. Among elderly men (≥70 years) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die from the comorbidities with prostate cancer present rather than from the cancer itself. Other very similarly appearing low-risk tumors may progress unexpectedly and rapidly, quickly disseminating and becoming incurable.

**Treatments**
The divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately. A patient may choose definitive treatment upfront. Surgery (radical prostatectomy) or external-beam radiotherapy are frequently used to treat patients with localized prostate cancer. Complications most commonly reported with radical prostatectomy or external-beam radiotherapy and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%).

American Urological Association guidelines have suggested patients with low- and intermediate-risk disease have the option of entering an “active surveillance” protocol, which takes into account patient age, patient preferences, and health conditions related to urinary, sexual, and bowel function. With this approach, patients forgo immediate therapy but continue regular monitoring until signs or symptoms of disease progression are evident—at which point curative treatment is instituted.

**Focal Treatments for Localized Prostate Cancer**
Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse events associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. This approach is termed focal treatment, in that it seeks to remove—using any of several ablative methods described next—cancerous lesions at high risk of progression, leaving behind uninvolved glandular parenchyma. The overall goal of any focal treatment is to minimize the risk of early tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum. Although focal treatments are offered as an alternative middle approach to manage localized prostate cancer, several key issues must be considered in choosing it. They include patient selection, lesion selection, therapy monitoring, and modalities used to ablate lesions.

**Patient Selection**
A proportion of men with localized prostate cancer have been reported to have (or develop) serious misgivings and psychosocial problems in accepting active surveillance, sometimes leading to inappropriately discontinuing it. Thus, the appropriate patient selection is imperative for physicians who must decide whether to recommend active surveillance or focal treatment.
for patients who refuse radical therapy or for whom it is not recommended due to the risk/benefit balance.25

**Lesion Selection**
Proper lesion selection is a second key consideration in choosing a focal treatment for localized prostate cancer. Although prostate cancer is a multifocal disease, clinical evidence has shown that between 10% and 40% of men who undergo radical prostatectomy for a presumed multifocal disease actually have a unilaterally confined discrete lesion, which, when removed, would “cure” the patient.26-28 This view presumably has driven the use of regionally targeted focal treatment variants, such as hemiablation of half the gland containing the tumor, or subtotal prostate ablation via the “hockey stick” method.29 While these approaches can be curative, the more extensive the treatment, the more likely the functional adverse outcomes would approach those of radical treatments.

The concept that clinically indolent lesions comprise most of the tumor burden in organ-confined prostate cancer led to the development of a lesion-targeted strategy, which is referred to as “focal therapy” in this evidence review.30 This involves treating only the largest and highest grade cancerous focus (referred to as the “index lesion”), which has been shown in pathologic studies to determine the clinical progression of the disease.31,32 This concept is supported by molecular genetics evidence that suggests a single index tumor focus is usually responsible for disease progression and metastasis.33,34 The index lesion approach leaves in place small foci less than 0.5 cm³ in volume, with a Gleason score less than 7, that are considered unlikely to progress over a 10- to 20-year period.35-37 This also leaves available subsequent definitive therapies as needed should disease progress.

Identification of prostate cancer lesions (disease localization) particularly the index lesion, is critical to the oncologic success of focal therapy; equally important to success is the ability to guide focal ablation energy to the tumor and assess treatment effectiveness. At present, no single modality reliably meets the requirements for all 3 activities (disease localization, focal ablation energy to the tumor, assessment of treatment effectiveness).25,30 Systematic transrectal ultrasound-guided biopsy alone has been investigated; however, it has been considered insufficient for patient selection or disease localization for focal therapy.38-42 See Blue Shield of California Medical Policy: Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer on saturation biopsy for prostate cancer for additional information.

Multiparametric magnetic resonance imaging (mpMRI), typically including T1-, T2-, diffusion-weighted imaging, and dynamic contrast-enhanced imaging, has been recognized as a promising modality to risk-stratify prostate cancer and select patients and lesions for focal therapy.24,30,38 Evidence has shown mpMRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping using a brachytherapy template.43 For example, for the primary end point definition (lesion, ≥4 mm; Gleason score, ≥3+4), with transperineal prostate mapping as the reference standard, sensitivity, negative predictive value, and negative likelihood ratios with mpMRI were 58% to 73%, 84% to 89%, and 0.3 to 0.5, respectively. Specificity, positive predictive value, and positive likelihood ratios were 71% to 84%, 49% to 63%, and 2.0 to 3.44, respectively. The negative predictive value of mpMRI appears sufficient to rule out clinically significant prostate cancer and may have clinical use in this setting. However, although mpMRI technology has the capability to detect and risk-stratify prostate cancer, several issues constrain its widespread use for these purposes (e.g., mpMRI requires highly specialized MRI-compatible equipment; biopsy within the MRI scanner is challenging; interpretation of prostate MRI images requires experienced uroradiologists) and it is still necessary to histologically confirm suspicious lesions using transperineal prostate mapping.44

**Therapy Monitoring**
Controversy exists about the proper end points for focal therapy of prostate cancer. The primary end point of focal ablation of clinically significant disease with negative biopsies evaluated at 12 months posttreatment is generally accepted according to a European consensus report.38 The
clinical validity of an MRI to analyze the presence of residual or recurrent cancer compared with histologic findings is offered as a secondary end point. However, MRI findings alone are not considered sufficient in follow-up.\textsuperscript{38} Finally, although investigators have indicated PSA levels should be monitored, PSA levels are not considered valid end points because the utility of PSA kinetics in tissue preservation treatments has not been established.\textsuperscript{35}

**Modalities Used to Ablate Lesions**

Five ablative methods for which clinical evidence is available are considered herein: focal laser ablation; high-intensity focused ultrasound; cryoablation; radiofrequency ablation; and photodynamic therapy.\textsuperscript{19,20,22,23,29,30,33,35,38,45,46} Each method requires placement of a needle probe into a tumor volume followed by delivery of some type of energy that destroys the tissue in a controlled manner. All methods except focal laser ablation currently rely on ultrasound guidance to the tumor focus of interest; focal laser ablation uses MRI to guide the probe. This evidence review does not cover focal brachytherapy (see Blue Shield of California Medical Policy: Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds).

**Focal Laser Ablation**

Focal laser ablation refers to the destruction of tissue using a focused beam of electromagnetic radiation emitted from a laser fiber introduced transperineal or transrectal into the cancer focus. The tissue is destroyed through thermal conversion of the focused electromagnetic energy into heat, causing coagulative necrosis. Other terms for focal laser ablation include photothermal therapy, laser interstitial therapy, and laser interstitial photocoagulation.\textsuperscript{47}

**High-Intensity Focused Ultrasound**

High-intensity focal ultrasound focuses high-energy ultrasound waves on a single location, which increases the local tissue temperature to over 80°C. This causes a discrete locus of coagulative necrosis of approximately 3×3×10 mm. The surgeon uses a transrectal probe to plan, perform, and monitor treatment in a real-time sequence to ablate the entire gland or small discrete lesions.

**Cryoablation**

Cryoablation induces cell death through direct cellular toxicity from disruption of the cell membrane caused by ice-ball crystals and vascular compromise from thrombosis and ischemia secondary to freezing below -30°C. Using a TPM template, cryoablation is performed by transperineal insertion under transrectal ultrasound guidance of a varying number of cryoprobe needles into the tumor.

**Radiofrequency Ablation**

Radiofrequency ablation uses energy produced by a 50-watt generator at a frequency of 460 kHz. Energy is transmitted to the tumor focus through 15 needle electrodes inserted transperineally under ultrasound guidance. Radiofrequency ablation produces an increase in tissue temperature causing coagulative necrosis.

**Photodynamic Therapy**

Photodynamic therapy uses an intravenous photosensitizing agent, which distributes through prostate tissue, followed by light delivered transperineally by inserted needles. The light induces a photochemical reaction that produces reactive oxygen species that are highly toxic and causes functional and structural tissue damage (i.e., cell death). A major concern with photodynamic therapy is that real-time monitoring of tissue effects is not possible, and the variable optical properties of prostate tissue complicate the assessment of necrosis and treatment progress.

**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 (QOL), 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, two 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.

This review only assesses evidence on focal therapy for primary localized prostate cancer; it does not consider the recurrent or salvage setting.

**Focal Therapy Overview**

**Clinical Context and Therapy Purpose**

The purpose of focal therapy using either laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation (RFA), or photodynamic therapy in men who have primary localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of focal therapy improve the net health outcome in men with primary localized prostate cancer?

The following PICOs were used to select literature to inform this review.

**Patients**

The relevant population of interest are men with primary localized prostate cancer.

**Interventions**

The therapy being considered is focal therapy using either laser ablation, high-intensity focused ultrasound, cryoablation, RFA, or photodynamic therapy.

Focal therapies are administered in an outpatient setting.

**Comparators**

The following therapies and practices are currently being used to make decisions about managing men with primary localized prostate cancer: surgery (radical prostatectomy), external-beam radiotherapy, and active surveillance.

**Outcomes**

The general outcomes of interest are overall survival (OS), tumor progression and recurrence, incontinence, and sexual dysfunction.

As a therapy situated between active surveillance and definitive therapy, focal therapy is a tissue-sparing procedure intended to maximize the QOL (e.g., incontinence, sexual dysfunction) by treating the index lesion. Thereafter, follow-up is conducted over at least ten years to monitor for tumor(s) progression and possible definitive therapy.
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.

No prospective, comparative studies were identified for any of the ablative technologies. The evidence comprises systematic reviews of noncomparative studies, case series, and other observational studies.

Systematic Reviews
A high-quality systematic review published by Valerio et al (2014) compiled the bulk of the evidence available in the literature on the technologies included herein through 2012. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Only studies that reported actual focal therapy procedures were included. Specific categories of data to be collected were prespecified. Study selection criteria were prespecified, with dual review and data extraction, and senior author arbitration as needed. The quality of included studies was assessed using the Oxford Centre for Evidence-based Medicine level of evidence for therapy. This review and its summarized statistics serve as the initial evidence source for this evidence review. Additional prospective studies of a comparative nature are reviewed in subsequent sections below.

Twenty-five series were included that evaluated a number of focal therapy methods used in the primary setting. The quality of evidence was low to medium, with no study yielding a level of evidence greater than 2b (individual cohort study). Twelve series used high-intensity focused ultrasound (n=226); 6 series (n=1400) used cryoablation (1 study included 1160 treated in the primary setting, 1400 total treated with cryoablation); 3 used focal laser ablation (n=16); 1 used RFA (n=14); and 1 used photodynamic therapy (n=6). In two series, focal treatments were mixed or included brachytherapy.

Patients in 12 series included had disease defined as low-risk (n=1109 [56%]), intermediate-risk (n=704 [36%]), and high-risk (n=164 [8%]); risk categories were not available in 13 series. The median age of patients ranged from 56 to 73 years. The prostate-specific antigen (PSA) level of patients ranged from 3.8 to 24 ng/mL. Individual Gleason scores were available in 20 series, with 1503 men having Gleason scores less than 6; 521 with Gleason scores of 7; and 82 had Gleason scores higher than 8. The median follow-up for the series ranged from 0 to 10.6 years. The disease was localized as follows: transrectal ultrasound biopsy in 2 series; transrectal ultrasound biopsy with Doppler ultrasound in 2 series; transrectal ultrasound biopsy plus magnetic resonance imaging in 6 series; transperineal template-guided mapping biopsy and multiparametric magnetic resonance imaging in 4 series; the preoperative assessment was not reported in 11 studies.

In all studies reporting such data in the Valerio et al (2014) systematic review, all known areas of cancer were treated; in no study was it explicitly stated the index lesion was ablated and that other lesions were left untreated. Biochemical control based on PSA levels was reported in five series using the Radiation Therapy Oncology Group-ASTRO Phoenix Consensus Conference criteria. Other definitions used to define biochemical control were American Society for Radiation Oncology (ASTRO; 5 series), Stuttgart (1 series), and Phoenix plus PSA velocity greater than 0.75 ng/mL annually (1 series). Biochemical control rates ranged from 86% at 8-year follow-up (n=318) to 60% at 5-year follow-up (n=56). Because follow-up was too short, progression to metastatic disease was not reported for most studies in the Valerio et al (2014) review; in those reporting follow-up data, metastatic progression rates were very low (0%
0.3%). Although a cancer-specific survival rate of 100% was reported in all series, such rates must be considered in the context of the small numbers of patients in individual studies and the short follow-up (only 3 studies had follow-up >5 years).

Across all studies, the median hospital length of stay was one day; other perioperative outcomes were poorly reported. Across studies, the most frequent complications associated with the treatment of prostate cancer—urinary retention, urinary stricture, and urinary tract infection—occurred in 0% to 17%, 0% to 5%, and 0% to 17%, respectively, of patients. Only five studies reported all three complications. Validated questionnaires were used in nine series to report urinary functional outcomes; physician-reported rates were used in five studies. According to the questionnaires, the pad-free continence rate varied between 95% and 100%, whereas the range of leak-free rates was 80% to 100%. Validated questionnaire data showed erectile functional rates in 54% to 100%, while physician-reported data showed erectile functional rates of 58% to 85%. Other adverse outcomes were poorly reported, particularly the QOL data, with only three studies reporting.

Wolff et al (2015) reported on results of a systematic review of RCTs of radiotherapy vs other nonpharmacologic treatments, including high-intensity focused ultrasound and cryoablation for the treatment of localized prostate cancer.51 The review followed the Centre for Reviews and Dissemination and Cochrane guidelines for conduct and reporting. The selection criteria and outcomes of interest were prespecified. The search included publications up to February 2014. Reviewers found two RCTs of cryotherapy vs radiotherapy but both evaluated whole-gland instead of focal cryotherapy and found no RCTs of high-intensity focused ultrasound vs radiotherapy.

### Laser Ablation

Additional case series and nonrandomized studies have assessed focal laser ablation, since the Valero et al (2014) review. Studies were small (range, 8-25 men), single-arm, lacked long-term follow-up (range, 3-6 months) and did not report clinical outcomes (e.g., progression-free survival, OS).

### Cryoablation

Lian et al (2016) reported on long-term results of a case series of 40 low- to intermediate-risk patients treated with primary focal cryoablation between 2006 and 2013 by a single urologist in China.54 Biochemical recurrence was defined using the Phoenix definition, and treatment failure was defined as at least one positive biopsy or biochemical recurrence. Mean follow-up was 63 months (range, 12-92 months). Two (5%) of 40 patients met the criteria for biochemical failure and 4 (10%) patients experienced treatment failure. Of the men who were potent before cryotherapy, 20 (77%) remained potent after treatment. Ninety-eight percent of the men were completely continent during follow-up.

A matched cohort study by Mendez et al (2015) included 317 men who underwent focal cryoablation with 317 men who underwent whole-gland cryoablation.55 Patients were entered into the Cryo Online Data Registry between 2007 and 2013. The median age at the time of the procedure was 66 years, and median follow-up was 58 months. All patients were preoperatively potent men who had low-risk disease according to the D'Amico risk criteria and were matched by age at surgery. Outcomes included biochemical recurrence-free survival, defined using ASTRO and Phoenix criteria and assessed by Kaplan-Meier curves. Only patients with PSA nadir data were included in oncologic outcome analysis. Functional outcomes were assessed at 6, 12, and 24 months after the procedure for erectile function (defined as the ability to have intercourse with or without erectile aids), urinary continence, urinary retention, and rates of fistula formation. After surgery, 30% (n=95) and 17% (n=55) of the men who underwent whole-gland cryoablation and focal cryoablation, respectively, underwent biopsy, with positive biopsy rates of 12% and 14%, respectively. Biochemical recurrence-free survival rates at 60 months using the Phoenix definition were 80% and 71% in the whole-gland and focal therapy cohorts, respectively, with a hazard ratio of 0.827 (p>0.1). Using the ASTRO definition, biochemical
recurrence-free survival rates were 82% and 73%, respectively (p>0.1). Erectile function data at 24 months were available for 172 whole-gland and 160 focal therapy-treated men. Recovery of erectile function was achieved in 47% and 69% of patients in the whole-gland and focal therapy cohorts, respectively (p=0.001). Urinary function data at 24 months were available for 307 whole-gland and 313 focal therapy patients. Urinary continence rates were 99% and 100% for the whole-gland and focal therapy groups, respectively (p=0.02). Urinary retention rates at 6, 12, and 24 months were reported as 7%, 2%, and 0.6%, respectively, in the whole-gland treated patients vs 5%, 1% and 0.9%, respectively, in the focal therapy cohort. One fistula was reported in each group.

The Cryo Online Data Registry is a database established and supported by a cryotherapy manufacturer. The data are maintained independently. Physicians submit standardized forms to the database and participation is voluntary. The registry contains case report forms of pretreatment and posttreatment information for patients undergoing whole-gland or partial-gland (focal) prostate cryoablation. Patients are stratified into low-, intermediate-, and high-risk groups. Ward and Jones (2012) have described characteristics of the focal cryotherapy registry patients.56 Biochemical success was defined using the ASTRO definitions. The analysis included 1160 patients treated with focal cryoablation and 5853 treated with whole-gland cryoablation between 1997 and 2007. Reports on the use of focal cryoablation increased dramatically between 1999 (46 reports) and 2005 (567 reports, p<0.01). The biochemical success at 36 months for focal cryotherapy was 75.7% and was similar to that of whole-gland cryoablation (75.5%); no significant differences between biochemical success for whole-gland and focal cryoablation were observed for low-, intermediate-, or high-risk groups (p-values not given). Urinary continence was 98.4% in focal and 96.9% in whole-gland cryoablation.

Photodynamic Therapy
Four-year results from a trial of TOOKAD, a soluble vascular-targeted photodynamic therapy (VTP), were reported by Gill et al (2018).57 A total of 413 men with low-risk prostate cancer were randomized and given biopsies at 12 and 24 months (206 in VTP plus active surveillance; 207 in active surveillance without VTP). Radical treatment was less likely at 24, 36, and 48 months ((hazard ratio, 0.31; 95% confidence interval, 0.21 to 0.46). At the risk difference between both arms was 36% (95% confidence interval, 28% to 44%), favoring men treated with VTP.

Summary of Evidence
For individuals who have primary localized prostate cancer who receive focal therapy using laser ablation, high-intensity focused ultrasound, cryoablation, RFA, or photodynamic therapy, the evidence includes a high-quality systematic review, studies from a registry cohort, and numerous observational studies. The relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, functional outcomes, QOL, and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. No prospective, comparative evidence was found for focal ablation techniques vs current standard treatment of localized prostate cancer, including radical prostatectomy, external-beam radiotherapy, or active surveillance. Methods have not been standardized to determine which and how many identified cancerous lesions should be treated for best outcomes. No evidence supports which, if any, of the focal techniques, leads to better functional outcomes. Although high disease-specific survival rates have been reported, the short follow-up periods and small sample sizes preclude conclusions on the effect of any of these techniques on OS rates. The adverse event rates associated with focal therapies appear to be superior to those associated with radical treatments (e.g., radical prostatectomy, external-beam radiotherapy); however, the evidence is limited in its quality, reporting, and scope. The evidence is insufficient to determine the effects of the technology on health outcomes.
Supplemental Information
Practice Guidelines And Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines for prostate cancer (v.2.2019) recommend cryosurgery or high-intensity focused ultrasound (HIFU) as options for radiotherapy recurrence for nonmetastatic disease; cryosurgery is not recommended for the initial treatment of localized prostate cancer.58.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2019) issued guidance on the use of cryoablation for localized prostate cancer.45 Cryoablation and high-intensity ultrasound are not recommended for the treatment of localized prostate cancer because there was a lack of evidence on quality-of-life benefits and long-term survival.

The National Institute for Health and Care Excellence (2014) issued guidance on the diagnosis and management of prostate cancer. The recommendations stated that neither cryotherapy or HIFU should be offered to men with localized prostate cancer or locally advanced prostate cancer outside of controlled trials comparing their use with established interventions.59.

American Urological Association et al
The American Urological Association, along with the American Society for Radiation Oncology and the Society for Urologic Oncology (2017) updated their joint guidelines on the management of clinically localized prostate cancer.16 The guidelines included the following recommendation on focal treatments:

“Clinicians should inform low-risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)”

“Clinicians should inform intermediate-risk prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)”

“Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial. (Expert Opinion)”

National Cancer Institute
The NCI (2018) updated its information on prostate cancer treatments.60 The NCI indicated that cryoablation and HIFU were new treatment options currently being studied in national trials. The NCI offered no recommendation for or against these treatments.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force published recommendations for prostate cancer screening.61 However, there are no recommendations for focal treatment of prostate cancer.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 1.
Table 1. Summary of Key Trials

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<td>Nov 2017 (ongoing)</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References

20. Nguyen CT, Jones JS. Focal therapy in the management of localized prostate cancer. BJU Int. May 2011;107(9):1362-1368. PMID 21223478

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<thead>
<tr>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.</td>
</tr>
</tbody>
</table>

IE
The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0582T</td>
<td>Transurethral ablation of malignant prostate tissue by high-energy water vapor thermotherapy, including intraoperative imaging and needle guidance <em>(Code effective 1/1/2020)</em></td>
</tr>
<tr>
<td></td>
<td>53854</td>
<td>Transurethral destruction of prostate tissue by radiofrequency generated water vapor thermotherapy <em>(Code effective 1/1/2019)</em></td>
</tr>
<tr>
<td></td>
<td>55899</td>
<td>Unlisted procedure, male genital system</td>
</tr>
<tr>
<td>HCPCS</td>
<td>C9747</td>
<td>Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance</td>
</tr>
</tbody>
</table>
Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/31/2015</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>11/01/2016</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>07/01/2017</td>
<td>Coding update</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>11/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>02/01/2019</td>
<td>Coding update</td>
</tr>
<tr>
<td>12/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>03/01/2020</td>
<td>Coding update</td>
</tr>
</tbody>
</table>

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 (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.

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.