MEDICAL POLICY

POLICY TITLE	TREATMENTS OF THE PROSTATE
POLICY NUMBER	MP 4.043

Original Issue Date (Created):	**4/1/2018**
Most Recent Review Date (Revised):	**06/14/2021**
Effective Date:	**7/1/2021**

I. POLICY

Use of any focal therapy modality as a treatment for the prostate is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Radiofrequency water vapor (steam) thermal therapy may be considered **medically necessary** when the following criteria is met:

- The individual is greater than or equal to50 has a diagnosis of benign prostate hypertrophy **and**
- A prostate volume greater than or equal to 30cm^3 and less than or equal to 80cm^3

Radiofrequency water vapor (steam) thermal therapy is consider **investigationa**l for prostate cancer. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

The prostatic urethral lift procedure (UroLift) may be considered **medically necessary** when the following criteria is met:

- The individual has a diagnosis of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) (e.g., increased urinary frequency, urgency, incontinence, or straining; nocturia; decreased and intermittent force of the stream; hematuria; and the sensation of incomplete bladder emptying) that interfere with activities of daily living; **and**
- The individual has a peak urine flow rate (Qmax) less than 15 cc/sec on a voided volume that is greater than 125 cc; **and**
- The individual has failed a trial of satisfactory voiding with medication (alpha blocker and/or alpha-reductase inhibitor) or intolerance to medication (alpha blocker and/or 5-alpha-reductase inhibitor); **and**
- When prostate size is no greater than 80 grams; **and**
- There is no median lobe enlargement present; **and**

- The patient has normal renal function **and**
- The patient has no known allergy to nickel; **or**
- In addition to the above criteria, if the individual has a diagnosis or history of prostate cancer and meets either of the following criteria:
  - The individual is not a candidate for surgical resection of the prostate but will be treated by radiation therapy and has symptoms that are so severe that immediate relief is required; **or**
  - The individual is clinically in remission as evidenced by a Prostate Specific Antigen (PSA) less than 1.0 ng/mL.

The prostatic urethral lift procedure is considered **investigational** for all other indications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Hydrogel Rectal Spacer
A hydrogel rectal spacer for prostate cancer may be considered **medically necessary** when the patient meets the following:

- Preparing to undergo radiation therapy for treatment of prostate cancer; **and**
- Has no MRI or other clinical evidence of posterior tumor extension onto or into the rectum.

Cross-reference:
MP-5.053 Magnetic Resonance–Guided Focused Ultrasound

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital BlueCross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Benefit Brochure for information on 7.01.164 Hydrocel Spacer Use During Radiotherapy for Prostate Cancer.

The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

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 (eg, 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).

For individuals who have primary localized prostate cancer who receive focal therapy using laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation, or photodynamic therapy, the evidence includes a high-quality systematic review, studies from a registry cohort, and numerous observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, 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 overall survival rates. The adverse event rates associated with focal therapies appear to be superior to those associated with radical treatments (eg., 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.

Prostate cancer is the second most common cancer diagnosed among men in the United States. According to the National Cancer Institute (NCI), nearly 240,000 new cases were to be 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. However, NCI Surveillance Epidemiology and End Results 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.

For low- or intermediate-risk prostate cancer, radiation therapy is an option. Because the rectum lies in close proximity to the prostate, the risk of rectal toxicity is high. One approach is to push the rectum away from the prostate, increasing the space and reducing the radiation dose to the rectum. A variety of biomaterials, including polyethylene glycol hydrogels (eg, SpaceOAR System) have been evaluated as perirectal spacers.

For individuals who have prostate cancer and are undergoing radiation therapy who receive a hydrogel spacer, the evidence includes a pivotal Randomized Control Trial (RCT) with a 3-year

follow-up, observational studies, and systematic reviews of these studies. Relevant outcomes include symptoms, quality of life, and treatment-related morbidity. The combined evidence indicates that the hydrogel spacer can reduce the radiation dose to the rectum with a statistically significant decrease in Grade 1 or greater late toxicity and anumber needed to treat of 14.3. There were few events of greater than Grade 1 toxicity in either group, and the number needed to treat for a reduction in clinically significant Grade 2 toxicity has been reported as 68. Patient-reported declines in rectal and urinary quality of life at three (3) years were statistically lower in the spacer group and met the threshold for a clinically significant difference, although patients were not blinded to treatment at the longer-term follow-up. The number needed to treat for late improvement in rectal and urinary quality of lifewere 6.3 to 6.7, respectively. Limitations to the study include the lack of blinding and the exclusion of patients who might be at greater risk of rectal toxicity. Evidence from observational studies is inconclusive, and potential benefits of the hydrogel spacer must be balanced against the risks of an additional procedure. Additional study are in progress to corroborate the findings of the pivotal RCT, to identify the factors that increase the risk of rectal toxicity, and to determine who is likely to benefit from the use of a spacer.

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 (eg, D'Amico criteria) or prognostic tools based on clinical findings (eg., 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 ten (10) years may range from 15% to 20%, ten (10) to perhaps 27% at 20-year follow-up. Among elderly men (greater or less than 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 similar 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 less than or equal to5%); 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, 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.

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 presumed multifocal disease actually have a unilaterally confined discrete lesion, which, when removed, would “cure” the patient. 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. 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 development of a lesion-targeted strategy, which is referred to as “focal therapy” in this evidence review. 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 clinical progression of disease.

This concept is supported by molecular genetics evidence that suggests a single index tumor focus is usually responsible for disease progression and metastasis. The index lesion approach

leaves in place small foci less than 0.5 cm3in volume, with a Gleason score less than 7, that are considered unlikely to progress over a ten (10)- to twenty (20) year period. 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). Systematic transrectal ultrasound–guided biopsy alone has been investigated; however, it has been considered insufficient for patient selection or disease localization for focal therapy. A 5-mm transperineal prostate mapping (TPM) biopsy using a brachytherapy template has been the recommended standard by the European Association of Urology, according to its 2012 guidelines. TPM can provide 3-dimensional coordinates of cancerous lesions, and has 87% to 95% accuracy rates in detecting and ruling out clinically significant cancer of all sizes. However, TPM is resource-intensive, requires general anesthesia, and has been associated with adverse events (including urinary retention [6%], prostatitis [4%], and local events such as perineal hematoma, bruising, and pain [5%]). The risk of complications of general anesthesia and the cost of processing multiple biopsy specimens limits the practicality and widespread applicability of this approach.

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 riskstratify prostate cancer and select patients and lesions for focal therapy. Evidence has shown mpMRI can detect high-grade, large prostate cancer foci with performance similar to TPM. For example, for the primary end point definition (lesion, greater than or equal to 4 mm; Gleason score, greater than or equal to3+4), with TPM 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 (eg, 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 TPM.

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. The clinical validity of 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.

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.

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. 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.

1. ***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. 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.

2. ***High-Intensity Focused Ultrasound***

High-intensity focused 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.

3. ***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.

4. ***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.

5. *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 (ie, 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 assessment of necrosis and treatment progress.

Transurethral Convective Water Vapor Thermal Ablation

Transurethral Convective Water Vapor Thermal Ablation (TUNA) using water vapor (ie., Rezūm System) delivers sterile water vapor (steam) transurethrally directly into hyperplastic tissue. Heat is released as the vapor condenses, causing cell death. The major difference between TUNA and Rezūm is how the Radiofrequency (RF) energy is delivered to the prostate. In both cases energy is transferred via a transurethral needle injection. With the former, RF energy is directly delivered to the prostate tissue in a conductive manner. This causes necrosis of the tissue. However, in the Rezūm system the RF energy is used to heat sterile water to vapor and steam which when injected convectively treats the prostate tissue. This latter mechanism is intended to be safer for the patient and yield improved results.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a common disorder among older men that results from hyperplastic nodules in the periurethral or transitional zone of the prostate. BPH prevalence increases with age and is present in more than 80% of men aged 70 to 79.[1] The clinical manifestations of BPH include increased urinary frequency, urgency, nocturia, hesitancy, and weak stream. The urinary tract symptoms often progress with worsening hypertrophy and may lead to acute urinary retention, incontinence, renal insufficiency, and/or urinary tract infection.

Two scores are widely used to evaluate BPH-related symptoms. The American Urological Association Symptom Index (AUASI) is a self-administered 7-item questionnaire assessing the severity of various urinary symptoms.[2] Total AUASI scores range from 0 to 35, with overall severity categorized as mild (less than or equal to7), moderate (8-19), or severe (20-35). The International Prostate Symptom Score incorporates the questions from the AUASI and a quality of life question or "Bother score."[3]

Management of BPH

Evaluation and management of BPH includes evaluation for other causes of lower urinary tract dysfunction (e.g., prostate cancer). Symptom severity and the degree that symptoms are bothersome determine the therapeutic approach.

Medical Therapy

A discussion about medical therapy is generally indicated for patients with moderate-to-severe symptoms (e.g., AUASI score, Greater than or equal to8), bothersome symptoms, or both. Available medical therapies for BPH-related lower urinary tract dysfunction include α-

adrenergic blockers (e.g., alfuzosin, doxazosin, tamsulosin, terazosin, silodosin), 5α-reductase inhibitors (e.g., finasteride, dutasteride), combination α-adrenergic blockers and 5α-reductase inhibitors, anti-muscarinic agents (e.g., darifenacin, solifenacin, oxybutynin), and phosphodiesterase-5 inhibitors (e.g., tadalafil).

Surgical and Ablative Therapies

Various surgical or ablative procedures are used to treat BPH. Transurethral resection of the prostate (TURP) is generally considered the reference standard for comparisons of BPH treatments. In the perioperative period, TURP is associated with risks of any operative procedure (e.g., anesthesia risks, blood loss). Although short-term mortality risks are generally low, one (1) large prospective study with 10,654 patients reported the following short-term complications: "failure to void (5.8%), surgical revision (5.6%), significant urinary tract infection (3.6%), bleeding requiring transfusions (2.9%), and transurethral resection syndrome (1.4%)." Incidental carcinoma of the prostate was diagnosed by histologic examination in 9.8% of patients. In the longer term, TURP is associated with risk of sexual dysfunction and incontinence.

Several minimally invasive prostate ablation procedures have also been developed, including transurethral microwave thermotherapy, transurethral needle ablation of the prostate, urethromicroablation phototherapy, and photo selective vaporization of the prostate.

Prostatic Urethral Lift

The prostatic urethral lift procedure involves placement of one (1) or more implants in the lateral lobes of the prostate using a transurethral delivery device. The implant device is designed to retract the prostate to allow expansion of the prostatic urethra. The implants are retained in the prostate to maintain an expanded urethral lumen.

One device, the NeoTract UroLift® System (NeoTract, Pleasanton, CA), has clearance for marketing by the U.S. Food and Drug Administration (FDA; see Regulatory Status section). The device has two (2) main components: the delivery device and the implant. Each delivery device comes preloaded with one (1) UroLift implant.

Outcome Measures Used in Evaluating BPH Symptoms

A number of health status measures are used to evaluate symptoms relevant to BPH and adverse effects of treatment for BPH, including urinary dysfunction, ejaculatory dysfunction, overall sexual health, and overall quality of life. Some validated scales are shown in Table 1.

Table 1. Health Status Measure Relevant to Benign Prostatic

Measure	Outcome Evaluated	Description	Clinically Meaningful Difference (If Known)
Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD)[6]	Ejaculatory function	Patient-administered, 4-item scale	
Sexual Health Inventory for Men (SHIM)[7]	Erectile function	Patient-administered, 5-item scale; final score range, 1 (worst symptoms) to 25 (fewest symptoms)	

American Urological Association Symptom Index (AUASI)[1,8]	Severity of lower urinary tract symptoms	Patient-administered, 7-item scale; final score range, 0 (no symptoms) to 35 (worst symptoms)	Minimum of 3-point change[1,8]
International Prostate Symptom Score (IPSS)[3]	Severity of lower urinary tract symptoms	Patient-administered, 8-item scale	
Benign Prostatic Hyperplasia Impact Index (BPH-II)[9,4]	Effect of urinary symptoms on health domains	Patient-administered, 4-item scale; final score range, 0 (best) to 13 (worst)	Minimum of 0.4-point change[8]
International Prostate Symptom Score (IPSS)[3]	Severity of lower urinary tract symptoms	Patient-administered, 8-item scale	
Benign Prostatic Hyperplasia Impact Index (BPH-II)[9,4]	Effect of urinary symptoms on health domains	Patient-administered, 4-item scale; final score range, 0 (best) to 13 (worst)	Minimum of 0.4-point change[8]
Benign Prostatic Hyperplasia Impact Index (BPH-II)[4,9]	Effect of urinary symptoms on health domains	Patient-administered, 4-item scale; final score range, 0 (best) to 13 (worst)	Minimum of 0.4-point change[8]

Hydrogel Spacer

For low-or intermediate-risk prostate cancer, radiation therapy is an option. Because the rectum lies in close proximity to the prostate, the risk of rectal toxicity is high. One approach is to push the rectum away from the prostate, increasing the space and reducing the radiation dose to the rectum. A variety of biomaterials, including polyethylene glycol hydrogels (eg, SpaceOAR System) have been evaluated as perirectal spacers.

Table 2. Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well-differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

REGULATORY STATUS

Focal Laser Ablation

In 2010, the Visualase® Thermal Therapy System (Medtronic, Minneapolis, MN) and, in 2015, the TRANBERGCLS|Laser fiber (Clinical Laserthermia Systems, Sweden) were cleared for

marketing by the FDA through the 510(k) process to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under magnetic resonance imaging guidance for multiple indications including urology, at wavelengths from 800 to 1064 nm. FDA product code: LLZ, GEX, FRN.

High-Intensity Focused Ultrasound

In 2015, the Sonablate® 450 (SonaCare Medical, Charlotte, NC) was approved by FDA through a de novo request and classified the device 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. A similar device, Ablatherm® (EDAP TMS, France), was cleared for marketing by FDA through the 510(k) process shortly thereafter.

Cryoablation

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

Radiofrequency (RF) Ablation

RF devices have been cleared for marketing by 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

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

Transurethral Convective Water Vapor Thermal Ablation

FDA has granted approval to the Rezūm System which delivers sterile water vapor (steam) transurethrally directly into hyperplastic tissue through the 510(k) process. FDA product code: KNS.

Prostatic Urethral Lift (PUL)

One implantable transprostatic tissue retractor system has been cleared for marketing by FDA through the 510(k) process. The NeoTract UroLift System (NeoTract, Pleasanton, CA) received clearance in December 2013 (after receiving clearance through FDA's de novo classification process in March 2013; K130651/DEN130023). In March 2016, FDA determined that the UL500 was substantially equivalent to existing devices (UL400) for the treatment of symptoms of urinary flow obstruction secondary to benign prostatic hyperplasia in men age 50 years and older. FDA product code: PEW.

SpaceOar Hydrogel Spacer

In October 2014, SpaceOAR® (Augmenix, a subsidiary of Boston Scientific) was cleared by the FDA through the De Novo process (DEN140030). "SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum."

III. RATIONALE

TOP

Summary of Evidence: Focal Treatment Overview

Systematic reviews have reported no published prospective, comparative evidence for focal ablation techniques versus current standard treatment of localized prostate cancer. Evidence consists of case series and noncomparative observational studies. Studies were generally small with short follow-up. Data on clinical outcomes such as progression to metastatic disease were not reported for most studies included in the Valerio review. Perioperative outcomes and other adverse events were also poorly reported.

For individuals who have primary localized prostate cancer who receive focal therapy using laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation, or photodynamic therapy, the evidence includes a high-quality systematic review, studies from a registry cohort, and numerous observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, 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 overall survival rates. The adverse event rates associated with focal therapies appear to be superior to those associated with radical treatments (eg, 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.

Summary of Evidence: Transurethral Convective Water Vapor Thermal Ablation Overview

The Rezūm System is substantially equivalent to the Prostiva Device (K113380/K142248). It has the same intended use for thermal ablation of BPH tissue. The test and clinical data showed that the technological difference between the Rezūm and its predicate do not raise safety and efficacy issues. The Rezūm II randomized placebo controlled clinical trial data showed that the device is effective in relieving the symptoms of BPH and does not raise new questions of safety. Based on

the test data and the same intended use, the Rezūm System is found to be substantially equivalent to its predicate.

Summary of Evidence: Prostatic Urethral Lift

For individuals who have lower urinary tract obstruction symptoms (due to BPH) and receive a PUL, the evidence includes systematic reviews, randomized controlled trials, and noncomparative studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. One randomized controlled trial, the BPH6 study, compared the PUL procedure with transurethral resection of the prostate and reported that the PUL procedure was noninferior for the study's composite end point, which required concurrent fulfilment of 6 independently validated measures of symptoms, safety, and sexual health. While transurethral resection of the prostate was superior to PUL in managing lower urinary tract symptoms, PUL did provide significant symptom improvement over 2 years. PUL was further superior to transurethral resection of the prostate in preserving sexual function. These findings were corroborated by another randomized controlled trial, entitled the LIFT study, which compared PUL with sham control. Patients underwent washout of BPH medications before enrollment. Lifestyle Interventions For Two (LIFT) reported that patients with the PUL procedure, compared with patients who had sham surgery and no BPH medication, had greater improvements in lower urinary tract symptoms without worsened sexual function at three (3) months. After three (3)- months, patients were given the option to have PUL surgery; 80% of the patients with sham procedures chose that option. Publications from this trial reported that functional improvements were durable over three (3), four(4) and five (5) -year follow-ups in a subset of patients treated with PUL; there was a high number of exclusions and loss to follow-up in that group. The evidence is sufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.2.2017) 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.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) issued guidance on the use cryoablation for localized prostate cancer in 2012. NICE concluded that current evidence on focal therapy using cryoablation for localized prostate cancer raises no major safety concerns. However, evidence on efficacy is limited in quantity, with concern that prostate cancer is commonly multifocal. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

NICE also issued guidance on the use of focal therapy using high-intensity focused ultrasound (HIFU) for localized prostate cancer in 2012. It concluded that current evidence on HIFU for localized prostate cancer raises no major safety concerns. However, evidence on efficacy is

limited in quantity, with concern that prostate cancer is commonly multifocal. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

In 2014, NICE issued guidance on diagnosis and management of prostate cancer. The recommendations stated that either 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.

In 2014, the National Institute for Health and Care Excellence published interventional procedural guidance on urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia. The guidance stated:

"Current evidence on the efficacy and safety of insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia is adequate to support the use of this procedure."

In 2015, the Institute published a medical technology guidance on the use of UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia.36 The guidance stated: "the UroLift system is effective in relieving symptoms of benign prostatic hyperplasia" and "the UroLift system should be considered as an alternative to current surgical procedures for use in a day-case setting in individuals with lower urinary tract symptoms of benign prostatic hyperplasia who are aged 50 years and older and who have a prostate of less than 100 ml without an obstructing middle lobe."

American Urological Association

The American Urological Association (AUA), along with the American Society for Radiation Oncology and the Society for Urologic Oncology, updated their joint guidelines on the management of clinically localized prostate cancer in 2017. 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)"

The AU) considers transurethral destruction of prostate tissue; by radio-frequency generated water thermotherapy, also known as the Rezum procedure, to be a viable treatment of BPH. Therefore, this procedure should be covered for reimbursement.
The 2010 (reaffirmed 2014) AUA guidelines on the management of BPH did not address the prostatic urethral lift procedure.

National Cancer Institute

The National Cancer Institute (NCI) updated its information on prostate cancer treatments in 2016. NCI indicates cryoablation and HIFU are new treatment options currently being studied in national trials. 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. However, there are no recommendations for focal treatment of prostate cancer.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02016040	Focal Therapy Using High Intensity Focused Ultrasound (AblathermÂ®) for Localized Prostate Cancer	25	Nov 2017 (ongoing)
NCT02328807	Focal Prostate Radio-Frequency Ablation for the Treatment of Prostate Cancer	30	Jun 2019
Unpublished			
NCT00877682*	Regional Cryoablation for Localized Adenocarcinoma of the Prostate	100	Jan 2018 (completed)
NCT02303054	MRI-US Fusion Biopsy-Guided Focal Radio-Frequency Ablation of the Prostate in Men with Localized Prostate Cancer (FUSAblate Trial)	21	Mar 2016 (completed)

NCT: national clinical trial.
*Denotes industry-sponsored or cosponsored trial.

Summary of Evidence for Hydrogel Spacer

For low or intermediate risk prostate cancer, radiation therapy is an option. Because the rectum lies in close proximity to the prostate, the risk of rectal toxicity is high. One approach is to push the rectum away from the prostate, increasing the space between the 2 and reducing the radiation dose to the rectum. A variety of biomaterials, including polyethylene glycol hydrogels (e.g., SpaceOAR System) have been evaluated as perirectal spacers.

For individuals who have prostate cancer and are undergoing radiation therapy who receive a hydrogel spacer, the evidence includes a pivotal RCT with a three (3)-year follow-up, observational studies, and systematic reviews of these studies. Relevant outcomes include symptoms, quality of life, and treatment-related morbidity. The combined evidence indicates that the hydrogel spacer can reduce the radiation dose to the rectum with a statistically significant

decrease in Grade I or greater late toxicity and anumber needed to treat of 14.3. There were few events of greater than Grade I toxicity in either group, and the number needed to treat for a reduction in clinically significant Grade II toxicity has been reported as 68. Patient-reported declines in rectal and urinary quality of life at three (3) years were statistically lower in the spacer group and met the threshold for a clinically significant difference, although patients were not blinded to treatment at the longer-term follow-up. The number needed to treat for late improvement in rectal and urinary quality of lifewere 6.3 to 6.7, respectively. Limitations to the study include the lack of blinding and the exclusion of patients who might be at greater risk of rectal toxicity.

In a study by Hamstra *et al*, SpaceOAR, a hydrogel intended to create a rectal prostate space, was evaluated in a single-blind phase III trial of image guided intensity modulated radiation therapy. A total of 222 men were randomized 2:1 to the spacer or control group and received 79.2 Gy in 1.8-Gy fractions to the prostate with or without the seminal vesicles. There was a median follow-up period of three (3) years. Cumulative toxicity, quality of life (QOL), and changes in the Expanded Prostate Cancer Index Composite (EPIC), were tested. The proportions of men with minimally important differences (MIDs) in each domain were tested using repeated measures logistic models with prespecified thresholds. The 3-year incidence of grade I (9.2% vs 2.0%; PZ.028) and grade 2 (5.7% vs 0%; PZ.012) rectal toxicity favored the spacer arm. Grade 1 urinary incontinence was also lower in the spacer arm (15% vs 4%; PZ.046), with no difference in grade2 urinary toxicity (7% vs 7%; PZ0.7). From 6 months onward, bowel QOL consistently favored the spacer group (PZ.002), with the difference at three (3) years (5.8 points; P less than .05) meeting the threshold for a MID. The control group had a 3.9-point greater decline in urinary QOL compared with the spacer group at three (3) years (P less than .05), but the difference did not meet the MID threshold. At three (3) years, more men in the control group than in the spacer group had experienced a MID decline in bowel QOL (41% vs 14%; PZ.002) and urinary QOL (30% vs 17%; PZ.04). Furthermore, the control group were also more likely to have experienced large declines (twice the MID) in bowel QOL (21% vs 5%; PZ.02) and urinary QOL (23% vs 8%; PZ.02). It is also notable that the use of this hydrogel spacer provided a clinically meaningful improvement even in the best current standard of care for conventionally fractionated dose-escalated RT, with Patient Reported Outcomes surveys (PROs) identifying significant improvements in both urinary and bowel QOL. (Hamstra, Daniel A; Mariados, Neil; Sylvester, John; and et al, ,"Continued benefit to rectal separation for prostate radiation therapy: Final results of a phase III trial." International journal of radiation oncology, biology, physics.97,5. 976-985. (2017). https://digitalcommons.wustl.edu/open_access_pubs/6031).

The SpaceOAR System (Augmenix, Inc., Bedford, MA) is an FDA approved absorbable hydrogel that can be introduced between the prostate and rectum to decrease rectal toxicity and minimize changes in bowel QOL. Prior analyses of the pivotal phase 3 trial noted lower penile bulb radiation dose with spacer, but there was no difference in average sexual QOL between arms; however, because nearly 60% of men who had moderate to severe sexual dysfunction at baseline, it is possible that an impact of the spacer on sexual function was masked. A post hoc analysis by Hamstra *et al* identified the subgroup of men with adequate baseline sexual QOL

(41% of respondents) and found a correlation between reduced RT dose to penile bulb and better sexual QOL as well as quality of erections when comparing the spacer arm with control.

Over a two-year period, hydrogel spacer use during radiation treatment in men with prostate cancer reduced GI, GU, and SD complications and yielded QALY gains at moderately increased costs meeting generally accepted definitions of cost effectiveness. (Brooks *et al*; 2020). Studies have shown that placement of the device between the prostate and rectum can optimize radiation therapies for patients with localized prostate cancer, and potentially minimize radiation-induced rectal toxicity and complications (Mariados 2015, Uhl 2014, Susil 2010). Those studies include a phase 3 trial that demonstrated a statistically significant reduction in late rectal toxicity (adverse events affecting the rectum, i.e., rectal bleeding) with the use of the spacer compared with rectal toxicity without spacer use (Mariados, et al, 2015).

Spacer application was rated as "easy" or "very easy" 98.7% of the time, with a 99% hydrogel placement success rate. Perirectal spaces were 12.6 ± 3.9 mm and 1.6 ± 2.0 mm in the spacer and control groups, respectively. There were no device-related adverse events, rectal perforations, serious bleeding, or infections within either group. Pre-to postspacer plans had a significant reduction in mean rectal V70 (12.4% to 3.3%, P less than .0001). Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain (P=.02). A significant reduction in late (3-15 months) rectal toxicity severity in the spacer group was observed (P=.04), with a 2.0% and 7.0% late rectal toxicity incidence in the spacer and control groups, respectively. There was no late rectal toxicity greater than grade I in the spacer group. At 15 months 11.6% and 21.4% of spacer and control patients, respectively, experienced 10-point declines in bowel quality of life. MRI scans at 12 months verified spacer absorption. Spacer application was well tolerated. Increased perirectal space reduced rectal irradiation, reduced rectal toxicity severity, and decreased rates of patients experiencing declines in bowel quality of life. The spacer appears to be an effective tool, potentially enabling advanced prostate RT protocols. *(*Mariados, et al, 2015).

National Comprehensive Cancer Network

The NCCN (V4:2019) provides the following recommendation in principles of radiation therapy, "Perirectal spacer materials may be employed when the previously mentioned techniques [highly conformal RT, photon or proton beam, brachytherapy boost] are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient-related factors, such as medication usage and/or comorbid conditions.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2017) published guidance on the biodegradable spacer. The National Institute for Health and Care Excellence concluded that "current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer is adequate to support the use of this procedure."

American Society of Clinical Oncology, the American Urological Association, and the American Society for Radiation Oncology

The American Society of Clinical Oncology, the AUA, and the American Society for Radiation Oncology (2018) published a joint guideline on hypofractionated radiation therapy for localized prostate cancer. The guideline recommends that men be counseled about the small increased risk of acute gastrointestinal toxicity with hypofractionation. "Moderately fractionated EBRT has a similar risk of acute and late genitourinary and late GI toxicity compared with conventionally fractionated EBRT. However, physicians should discuss the limited follow-up beyond five (5) years for most existing RCTs [randomized controlled trials] evaluating moderate hypofractionation." This was a strong recommendation based on high-quality evidence and 100% consensus.

IV. DEFINITIONS

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IMRT refers to Intensity Modulated Radiation Therapy.

QALY refers to Quality Adjusted Life Year.

QoL refers to Quality of Life.

V. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VI. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational when used to describe Focal Treatments for Prostate Cancer

CPT Codes®							
0582T	55899	55880	0655T				

HCPCS Codes	Description
C2596	Probe, image-guided, robotic, waterjet ablation
C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance
C9761	Cystourethroscopy, with ureteroscopy and/or pyeloscopy, with lithotripsy, and ureteral catheterization for steerable vacuum aspiration of the kidney, collecting system, ureter, bladder, and urethra if applicable
C9769	Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts.

Covered when Medically Necessary when used for Radiofrequency water vapor (steam) thermal therapy

CPT Codes®							
53854							

ICD-10-CM Diagnosis Code	Description
D29.1	Benign Neoplasm of Prostate
N13.8	Other Obstruction and Reflux Uropathy
N32.0	Bladder Neck Obstruction
N40.1	Enlarged Prostate with lower urinary tract symptoms
N40.3	Nodular Prostate with lower urinary tract symptoms
R33.8	Other Retention of Urine
R39.15	Urgency of Urination
R39.16	Straining to Void

Covered when Medically Necessary for Prostatic Urethral Lift

CPT Codes®								
52441	52442							

HCPCS Code	Description
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants

ICD-10-CM Diagnosis Code	Description
D29.1	Benign Neoplasm of Prostate
N40.1	Enlarged Prostate with lower urinary tract symptoms
N40.3	Nodular Prostate with lower urinary tract symptoms

Covered when Medically Necessary for Hydrogel Therapy

CPT Codes®							
55874							

ICD-10-CM Diagnosis Code	Description
C61	Malignant Neoplasm of Prostate
C79.82	Secondary malignant neoplasm of genital organs
D07.5	Carcinoma in situ of prostate
D40.0	Neoplasm of uncertain behavior of prostate
D49.59	Neoplasm of unspecified behavior of other genitourinary organs

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 4.043	**CAC 11/28/17** New policy, adopted BCBSA. Use of any focal therapy modality to treat patients with localized prostate cancer is investigational. FEP variation added. Coding added.
	5/25/18 Minor review. New criteria added for radiofrequency water vapor (steam) thermal therapy to be medically necessary for benign prostate hypertrophy. UroLift policy criteria added to make a further encompassing prostate policy. Title changed to Treatments of the Prostate. Coding updated. Added new code 53854 effective 1/1/19. Noted C9748 will be effective through 12/31/18.
	4/3/19 Minor review. Criteria change made to UroLift, other policy statements unchanged. References updated. Removed expired coding, C9748.
	1/1/20 Administrative update. Added new code 0582T & C2596.
	4/3/20 Consensus review. Policy Statement unchanged. ICD codes: N13.8; R33.8; R39.15; R39.16 added and updated. References reviewed and updated. Variations updated.
	7/16/2020 Minor Review. Policy Statement changed to include the Hydrogel Spacer. Variation Statement updated. References reviewed, updated and Hydrogel Spacer references added. Coding reviewed. New codes added: 55874; c61; C79.82; D07.5; D40.0; D49.59.
	11/18/20: Administrative update. Added code 55880. Effective 1/1/21
	12/14/2020 Administrative update. Deleted code C9747. Effective 1/1/2021.
	3/10/2021: Administrative update. Revised Code C9761. Effective 4/1/2021.
	6/14/2021: Admin review. Added code 0655T to INV focal treatments. Effective 7/1/2021.

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