MEDICAL POLICY	Prostate: Benign Prostatic Hyperplasia Treatments (All Lines of Business Except Medicare)
Effective Date: 7/1/2022  7/1/2022 Medical Officer Date	Medical Policy Number: 246 Medical Policy Committee Approved Date: 9/19; 10/2020; 3/2021; 11/2021; 6/2022

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All Lines of Business Except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Water Vapor Thermoplasty

I. Water vapor thermotherapy (i.e. Rezūm System) may be considered **medically necessary** or the treatment of benign prostatic hyperplasia (BPH) when all of the following criteria (A.-E.) are met:

   A. Patient is at least 50 years of age; **and**
   B. Patient has moderate-to-severe chronic lower urinary tract symptoms (defined as an American Urologic Association or International Prostate Symptom Score $\geq$ 8); **and**
   C. Pharmacologic BPH treatment has been unsuccessful or intolerable; **and**
   D. Prostate volume is at least 30 cm^3; **and**
   E. Prostate volume is no greater than 80 cm^3.

II. Water vapor thermotherapy (i.e., Rezūm System) is considered **investigational and not covered** when criterion I. above is not met.

Prostatic Urethral Lift

III. The prostatic urethral lift (PUL) procedure (i.e. UroLift®) may be considered **medically necessary** for the treatment of symptomatic benign prostatic hyperplasia (BPH) when all of the following criteria (A.-D.) are met:

A. Patient is age 45 or older; and
B. Patient has moderate-to-severe chronic lower urinary tract symptoms (defined as an American Urologic Association or International Prostate Symptom Score ≥8); and
C. Pharmacologic BPH treatment has been unsuccessful or intolerable; and
D. Patient meets all of the following indications for the PUL procedure (1.-6.):
    1. Has a prostate volume less than 100cc; and
    2. Does not have an obstructive or protruding median lobe of the prostate; and
    3. Does not have a urethra condition that may prevent insertion of delivery system into bladder; and
    4. Does not have an active urinary tract infection (UTI); and
    5. Does not have current gross hematuria; and
    6. Urinary incontinence is not due to an incompetent sphincter.

IV. The prostatic urethral lift is considered **investigational and not covered** when criterion III. above is not met.

V. Repeat prostatic urethral lift procedures are considered **medically necess**ary when criterion III. (A-D) is met.

Investigational Treatments of BPH

VI. Transurethral waterjet ablation (e.g., AquaBeam by Procept BioRobotics) is considered **investigational and not covered** for the treatment of benign prostatic hyperplasia.

VII. Transperineal laser ablation is considered **investigational and not covered** for the treatment of benign prostatic hyperplasia.

Link to Policy Summary

CPT/HCPCS CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
53854	Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy
52441	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant
52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants
Not Covered	
0421T	Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)
0714T	Transperineal laser ablation of benign prostatic hyperplasia, including imaging guidance
C2596	Probe, image-guided, robotic, waterjet ablation
Unlisted All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be **denied as not covered.**	
53899	Unlisted procedure, urinary system

DESCRIPTION

Benign Prostatic Hyperplasia

Benign Prostatic Hyperplasia (BPH) is an enlargement of the prostate gland. The prostate gland sits below the bladder and encircles the urethra (the tube that carries urine out of the body). The prostate naturally grows with age, and as it grows it can begin to compress the urethra and because of this, BPH is very common in aging men. Approximately 50% of all men age 51 to 60 have BPH, and approximately 90% of men over the age of 80 have BPH.[1] Many men with BPH do not have symptoms. Men that do have symptoms usually experience frequent urination, a weak urine stream, and/or leaking urine. These BPH symptoms are commonly referred to as lower urinary tract symptoms (LUTS). The treatment for LUTS usually depends on the severity of symptoms. Men with mild BPH may start with life style changes; while men with moderate-to-severe BPH typically require treatment with medications and possibly surgery.[2]

Treatment of Benign Prostatic Hyperplasia

Pharmacologic Therapy

There are two types of medicines used to treat BPH: alpha blockers and alpha-reductase inhibitors. Typically, men who start taking BPH medicine will need to take it forever unless surgical treatment is undertaken.[2] Alpha blockers may be used to treat LUTS related to BPH by relaxing the muscles of the prostate and bladder neck; thus reducing the pressure on the urethra and more urine flow. Alpha blockers begin to work quickly and are usually recommended as the first-line of treatment for mild-to-moderate BPH symptoms.[2] Alpha-reductase inhibitors stop the prostrate from growing and can even cause it to shrink. This type of medication is recommended for men with larger prostates and can take up to six months for symptom improvement. Common side effects of both BPH medicines include dizziness, loss of libido, and sexual dysfunction. These side effects and the need for life-long BPH medication compliance, lead 30% of men to discontinue their BPH medicine after the first year.[3]

Transurethral Resection of the Prostate (TURP)

TURP is a surgical treatment for BPH that involves the removal of obstructing tissue from the prostate. In the United States, about 150,000 men have TURPs each year.[4] The procedure is typically performed under general or spinal anesthesia and requires a 24-48 hour postoperative catheterization observation period. The average recovery time after the TURP procedure is anywhere from 4 to 12 weeks, and patients may also experience a postoperative worsening of LUTS for 4 to 6 weeks. On average, TURP results in a 14.9 International Prostate Symptom Score (IPSS) improvement; therefore making it the gold standard surgical intervention for treatment of BPH.[5] However, due to the invasive nature of the TURP procedure it is associated with more serious and possibly chronic complications including loss of ejaculatory function (65%), erectile dysfunction (10%), incontinence (3%), excessive bleeding requiring transfusion (2.9%), transurethral resection syndrome (1.4%), and stricture formation (7%).[5,6] Although the TURP procedure significantly improves LUTS, these potential adverse side effects could considerably impact a patient's quality of life; therefore, new surgical techniques have been proposed as less invasive alternatives to TURP.

The Rezum System

According to Hayes:

> "The Rezum System [i.e. Rezum] is a minimally invasive, transurethral treatment for BPH that utilizes convective radiofrequency water vapor energy to ablate the hyperplastic tissue. The Rezum System consists of a radiofrequency power generator and a disposable delivery device. The rigid shaft of the delivery device incorporates a standard lens so that the procedure may be performed under cystoscopic visualization. The delivery device also contains a needle, which injects wet thermal energy (i.e., steam) into diseased prostatic tissue. The steam immediately condenses to water thereby dispersing thermal energy and killing the surrounding cells. The dead cells are eventually absorbed, which reduces the volume of prostatic tissue and opens the

urethra … Once the Rezum delivery device is within the prostate, the needle is deployed and a 9-second burst of 103˚C water vapor is injected into the prostatic tissue creating a spherical lesion of 1.5 to 2 centimeters (cm). The total number of treatments in each lobe is based upon the length of the hyperplastic prostatic tissue and the length of the urethra, but typically 1 to 3 sites are treated per lobe. The goal is to create contiguous, overlapping lesions approximately 1 cm apart along the urethra."[7]

Prostatic Urethral Lift (PUL) (UroLift®)

The PUL procedure (i.e. UroLift®) is a surgical treatment for BPH that involves the placement of small mechanical sutures which hold the enlarged prostate tissue out of the way so it no longer blocks the urethra.[8] This is done by placing small, non-absorbable suture implants with a metallic anchor into the lateral (side) lobes of the prostate. These sutures mechanically separate the lobes in order to help relieve pressure and increase the opening of the urethra. Four to five implants are usually inserted, but this number varies with the size and shape of the prostate.10 Since the PUL procedure does not remove any obstructing prostate tissue and typically only requires local anesthesia, it is less invasive than other surgical BPH treatments. PUL is typically performed in the doctor's office by an appropriately trained urologist.

Transperineal Laser Ablation

Transperineal Laser Ablation is an alternative to other minimally invasive treatments for BPH. Unlike Holmium or thulium laser enucleation, the treatment is transperineal rather than transurethral—that is, the surgeon uses a percutaneous approach through the skin of the perineum, between the patient's genitals and anus.[9]

REVIEW OF EVIDENCE

Water Vapor Thermoplasty

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of the Rezum System (NxThera Inc.) as a treatment for benign prostatic hyperplasia. Below is a summary of the available evidence identified through September 2021.

Systematic Reviews

- In 2019 (archived in 2021), Hayes conducted an evidence review evaluating the safety and efficacy of the Rezum System for the treatment of benign prostatic hyperplasia (BPH).[7] Searching the literature through February, Hayes included 8 publications for review. The publications reported data from 4 clinical studies (1 randomized, sham-controlled study, and 3 pretest-post-test studies.) Sample sizes across studies ranged from 65 to 197. Primary outcomes of interest included urinary symptoms, health-related quality of life, sexual function, safety and treatment failure. Results across 4 studies suggested that, compared to the sham group, Rezum patients' LUTS and quality of life significantly improved from baseline at 3-years' follow-up (50%

vs. 20%; p < 0.0001). Measures of clinically meaningful response ranged from 67% to 85% at 12-month follow-up. No significant effect on sexual function was reported across either Rezum or sham patients. Adverse events and failure rates were also minimal.
Hayes judged the overall quality of evidence to be of "very-low," concluding that Rezum may relieve lower urinary tract symptoms (LUTS) associated with BPH and improve patients' health-related quality of life at up to 3 years. Limitations across studies may undermine results' validity, however. Individual studies suffered from small sample sizes, a lack of comparison groups, a lack of long-term follow-up, and substantial loss to follow-up. Hayes ultimately assigned a "D2" rating (insufficient evidence) for use of Rezum in men with LUTS secondary to BPH. Investigators stated that, in addition to unestablished patient selection criteria, "substantial uncertainty remains regarding [Rezum's] comparative effectiveness and safety due to a lack of comparative studies, as well as limited long-term evidence regarding the durability and safety."[7]

- In 2016 (updated 2019), ECRI conducted an evidence review assessing the safety and efficacy of Rezum for the treatment of benign prostatic hyperplasia.[10] Searching the literature through March 2019, ECRI reviewed the full texts of 1 RCT and 3 pre-post studies reporting outcomes for 522 patients. The RCT included for review is the evaluated below.[11] The pre-post studies are the same as those evaluated in the Hayes review discussed above.[7] ECRI concluded that the balance of evidence regarding Rezum's efficacy is "somewhat favorable," with statistically and clinically significant improvements in patients' LUTS and quality of life across all studies. Investigators noted that study limitations may undermine results' validity, noting the limited quantity of RCTs comparing Rezum to a sham procedure (n =1), and the absence of any RCTs comparing Rezum to any other BPH treatment. Sham procedures and pre-post studies were also vulnerable to placebo effects due to the lack of blinding. In the case of the sham procedure, LUTS may also decrease due to temporary urethral dilation caused by rigid cystoscopy, although the placebo effect is thought to dissipate within 6 months. The reviewed pre-post studies also included patients with prostate volumes smaller or larger than described in the FDA-labeled indication (30 to 80cm3), which may have generated results different from reported findings in the on-label population. ECRI concluded that additional studies comparing Rezum to alternative treatments were necessary (e.g. transurethral resection of the prostate, microwave ablation, prostatic urethral life) so as to more definitively establish Rezum's safety and efficacy.

- In 2020, Miller et al conducted an industry-funded systematic review and meta-analysis of water vapor thermal therapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia.[12] Five cohorts from 4 studies were reviewed, reviewing data from 514 total. The review found that international prostate symptom score, IPSS quality of life, benign prostatic hyperplasia impact index, and maximum flow rate were all improved from baseline. Surgical treatment rates were 2.4% at year one, 5.3% at year 2, 6.3% at year 3, and 7.0% at year 4 of follow-up. These studies, already reviewed in the above Hayes and ECRI reports, and this review suffer from a number of limitations. Only one study was randomized, and only participants receiving water vapor thermal therapy were included in analysis. The other 4 studies were small, had short follow-up and had high heterogeneity. There was no comparator, and no conclusions can be made about the efficacy of water vapor thermal therapy compared to standard of care treatments.

Randomized Controlled Trials

In 2019, McVary and colleagues conducted a manufacturer-funded randomized controlled trial reporting lower urinary tract symptoms (LUTS) associated with BPH in patients receiving Rezum.[11] In total, 188 patients with International Prostate Symptom Score ≥13, with a maximum flow rate (Qmax) ≤ 15mL/s and prostate volume 30 to 80cc were treated and followed for 4 years. A subset of 53 patients who initially received sham treatment "crossed over" to active treatment after unblinding at 3-months. This group was followed for 3 years. Results indicated significant improvement in both groups' LUTS and quality of life within 3 months of treatment, sustained throughout 4 years ($p < 0.0001$). Results' validity may be limited by the investigators' financial conflicts of interest with Rezum's manufacturer, the lack of treatment groups receiving an alternative BPH therapy, narrow inclusion criteria (e.g. all patients 50 years old, without history of urinary retention or UTI) and significant loss to follow-up (primary group: 32.8%, n = 44/134; cross-over group 45.3% n = 24/53). Investigators concluded that Rezum can provide effective symptom relief and improve quality of life for patients with BPH.

Prostatic Urethral Lift (PUL)

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of prostatic urethral lift procedure (PUL) (UroLift®) as a treatment for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Below is a summary of the available evidence identified through September 2021.

Systematic Reviews

- In 2019, Cochrane published a systematic review evaluating the safety and efficacy of prostatic urethral lift (PUL) for the treatment of lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH).[13] Systematically searching the literature through January 2019, investigators identified eligible studies, assessed study quality, extracted data and pooled results. Inclusion criteria were limited to parallel group RCTs. In total, 2 RCTs (n=297) comparing PUL to either sham surgery or TURP were included for review. Outcomes of interest included LUTS scores, quality of life, erectile function, ejaculatory function, adverse events and retreatment rates. The study comparing PUL to sham treatment reported clinically significant improvements in PUL patients' urological symptom scores and quality of life. No significant difference was reported in patients' erectile function or ejaculatory function. Evidence of adverse events was assessed as being of "very low certainty"; no retreatments were reported in either treatment arm at 3-month followup. The study comparing PUL to TURP reported outcomes of 91 randomized patients at 12-months follow-up. Investigators concluded that PUL "may result" in substantially less improvement in urological symptom scores relative to TURP, and in comparable or slightly reduced quality of life. Evidence was "very uncertain" regarding whether PUL may cause fewer major adverse events but increased retreatments. At 2-year follow-up, compared to TURP, PUL patients experienced substantially less improvement in urological symptom scores and "little worse to no difference" quality of life scores.

Limitations of studies included lack of blinding in participants and assessors, lack of long-term follow-up and lack of published RCTs more broadly. Due to the paucity of evidence, investigators were unable to perform any of the predefined secondary analyses for either comparator group. Authors concluded that PUL appears to be less effective than TURP in improving urological symptoms at short-term follow-up (i.e. ≤ 2 years). Evidence was uncertain regarding major adverse events, retreatment rates, erectile function and ejaculatory function. Investigators called for additional, higher-quality studies comparing PUL to TURP and other treatment modalities with long-term follow-up.

- In 2019, ECRI published a systematic review[14] assessing evidence published since their (abovementioned) 2017 review (discussed below). Investigators limited literature searches to between May 2016 and June 2019. In total, ECRI included 3 studies for review (2 case series, 1 cost-effectiveness study). The first case series reported on international prostate symptom score (IPSS), quality of life, BPH impact index (BPHII) and sexual function among 45 patients with obstructive median lobes at 1-year follow-up.10 Limitations included the study's small sample size, lack of long-term follow-up, "significant differences"10 among patients' characteristics at baseline, lack of randomization, blinding and a comparator group. The second case series reported pre- and postprocedure outcomes at 5-year follow-up for 87 patients allocated to the prostatic urethral lift treatment arm of the LIFT study discussed below. The study's validity was limited by its small sample size, but reported 36% superior IPSS improvement compared to patients receiving sham treatment, as well as 61% comparative improvement in quality of life and 70% comparative improvement in BPHII. Investigators concluded that evidence is "somewhat favorable" in support of PUL compared to sham treatment in improving LUTS and quality of life. Nonetheless, authors called for additional RCTs comparing PUL to TURP to further validate findings, assess long-term efficacy, and assess overall efficacy in patients with median lobe obstruction.

- In 2017, ECRI published a health technology assessment of the UroLift® procedure for treating BPH symptoms.[15] The authors systematically searched for relevant research published between January 2011 and October 2016 and included three systematic reviews and two randomized controlled trials (RCTs). The evidence suggested that the UroLift® procedure was well-tolerated and works as intended for treating BPH symptoms in most patients for up to three years.11 The ECRI authors also identified the potential benefit of UroLift® for preserving sexual function and quality of recovery compared to TURP. However, 10.7% of UroLift® treated patients experienced treatment failure that required surgical re-intervention. The assessment also noted that 363 UroLift-related complications had occurred across 7 studies, but more than 95% of these complications resolved without medical intervention. Ultimately, the ECRI assessment acknowledged the promising technology of the UroLift procedure, but concluded that future RCTs are needed to confirm the results.

- In 2020 (updated in 2021), Hayes published a systematic review which included 9 clinical studies (1 sham-controlled randomized controlled trial (RCT), 1 RCT comparing PUL with TURP, and 7 single-arm observational studies)) that evaluated the efficacy and safety of the PUL procedure using the UroLift® system for treatment of LUTS related to BPH.[16] The systematic review

suggested that PUL was superior to TURP in regards to improvement of the International Prostate Symptom Score (IPSS) and Benign Prostatic Hyperplasia Impact Index (BPHII), early relief of BPH symptoms, and preserving sexual function. However, TURP was reported as superior to UroLift® at improving post-void residual volume (PVR) and peak urinary flow rate (Qmax). The included studies reported minor adverse events, such as dysuria (pain when urinating), hematuria (blood in urine), pelvic pain, and urinary tract infections (UTIs). Hayes stated that the UroLift® device does not appear to compromise sexual function and that the adoption of this device, in appropriately selected patients, may reduce the utilization of inpatient hospital services that are required for more invasive procedures; both of which were reported as significant advantages of this device compared to TURP. Hayes considered the studies included in the review to be of low-quality due to small sample sizes, limited follow-up time, and losses to follow-up. Hayes gave an overall "C" rating for use of the UroLift® System as a treatment of LUTS caused by BPH. This rating was based on the low-quality body of evidence noted above and the, "substantial uncertainty that remains due to the dearth of comparative studies and limited long-term evidence regarding the durability and safety of this device."[16]

- In 2016, Jones et al. conducted a good-quality systematic review to identify, appraise, and synthesize the existing evidence for the UroLift® device to treat LUTS secondary to BPH.[17] Two independent reviewers conducted a systematic literature search following pre-defined inclusion/exclusion and quality criteria. Ultimately 7 studies (2 RCTs, 1 crossover trial, and 4 cohort studies) were selected for inclusion, with a total of n=440 patients included. The authors divided the outcome measures of the selected studies into two categories: objective (measurable) outcomes and subjective (opinion based) outcomes. The objective outcome measures included prostatespecific antigen (PSA), post-void residual (PVR) volume, and maximum urinary flow rate (Qmax). The subjective outcome measures included in the systematic review were the International Prostate Symptom Score (IPSS), Quality of Life (QoL), International Index of Erectile Function (IIEF), and Sexual Health Inventory for Men (SHIM).

  The UroLift® procedure exhibited improvements in both objective and subjective outcome measures; however, the most significant improvements were in the subjective measures. Unlike TURP, the UroLift® did not demonstrate significant, long-term improvements in PVR and Qmax. The authors suggested that studies with longer follow-up periods were needed to confirm its durability MEDICAL POLICY Prostate: Prostatic Urethral Lift Page 6 of 13 MP161 and long-term efficacy. The review also evaluated the UroLift® safety profile in the selected studies. Authors reported the UroLift had favorable advantage over TURP in the ability to preserve sexual function. The authors also recognized that careful patient selection was vital when choosing to perform UroLift, given all the explicit indications for the procedure, and that the efficacy and safety had yet to be proven among men with more complicated health problems.

  There were several strengths of this systematic review, including the selection of high quality studies which were published within the last 5 years and the systematic approach taken for selecting literature and extracting data. Limitations of this systematic review were due to the limited number of quality studies on the UroLift® procedure and the inability to conduct a meta-analysis because the selected studies varied in type and quality. Ultimately, the authors

concluded that the UroLift® procedure, "may not be an end-of-the-line intervention but rather, an intermediate, minimally invasive option for a specific population of men who wish to preserve sexual function as a key priority in their treatment."[17]

- In 2020, Miller and colleagues published a systematic review and meta-analysis on surgical reintervention rates after prostatitic urethral lift.[18] Eleven studies totalling 2016 patients were included in the analysis. Nine studies were observational (4 of which were prospective), and 2 were RCTs (one comparing PUL to TURP and another comparing PUL to sham procedures). All studies were also analyzed in the Hayes review above. The authors found that 153 surgical interventions were performed, 51.0% were TURP, 32.7% were repeat PUL, and 19.6% were device explant. The annual rate of reintervention was 6.0% per year (95% CI, 3.0-8.9). Studies with longer follow up were found to have higher rates of reintervention. The authors note that the medical literature often states that reintervention rates after PUL are around 2-3%, likely due to the fact that they do not include device explant in their data analyses. This study highlights the limitations of studies with short-term follow up and the need comparator trials with long term follow up to determine true rates of reintervention and the burden this has on patients.

- In 2020, Tanneru and colleagues published a meta-analysis and systematic review of intermediate-term follow-up of prostatic urethral lift for benign prostatic hyperplasia.[19] Five studies (totalling 386 patients) with a minimum of 24 months were included in the analysis. After 24 months, mean reduction in International Prostate Symptom Score (IPSS) was 9.1 in the two randomized trials (185 patients) and 10.4 in the 3 nonrandomized studies (201 patients). Quality of life scales improves by 2.2 in an analysis of both randomized and non-randomized trials. The authors noted that there is a paucity of trials investigating PUL with long term follow up, and most available studies have small sample sizes. They concluded that PUL appears to be safe and effective for select patients with BPH, but more studies with longer follow up are needed to determine the permanency of these results.

Randomized Controlled Trials (RCTs)

- The L.I.F.T. study (Luminal Improvement Following Prostatic Tissue Approximation for the Treatment of LUTS secondary to BPH) was a prospective, randomized, controlled, blinded study conducted across 19 centers in the United States, Canada, and Australia.[20] Participants were eligible for inclusion under the following criteria:
    1. >50 years old
    2. IPSS ≥13
    3. Peak flow (Qmax) ≤12 mL/s
    4. Prostate volume 30-80cc
    5. Absence of obstructive median lobe
    6. Absence of active UTI

  A total of 206 participants were enrolled and randomized 2:1 into the treatment (PUL) and sham groups (PUL=140, sham=66). Blinding was done by placement of a surgical screen to block the

patient's view and the outcome assessment was completed by someone who was not involved in the original procedure. The sham procedure involved rigid cystoscopy (a procedure to check for any problems in the bladder) with simulated active treatment sounds. PUL participants received anywhere from 2-11 implants. The outcomes of interest were IPSS, QoL, BPH Impact Index, Qmax, sexual function, and adverse events. After the 3 month follow-up, the sham patients were unblinded and offered enrollment into a crossover study where they would receive PUL treatment and be followed for 24 months (Rukstalis et al. study described below).

The L.I.F.T. RCT is now reporting results on effectiveness, safety, and durability from their 5 year follow-up. The effectiveness of the PUL procedure in regards to IPSS, QoL, BPH Impact Index, and Qmax has been sustained through 5 years. The most significant adverse event reported was encrustation of the implant(s) caused by urine exposure when placed too close to the bladder. Of the 642 implants placed during the L.I.F.T. study, 14 implants (2%) in 10 subjects were encrusted and had to be removed. Other reported adverse events were mild-to-moderate and resolved within 2-4 weeks without treatment. In regards to durability of the UroLift® procedure, 13.6% of the 140 originally enrolled subjects required surgical retreatment. Conversely, additional LUTS treatment after TURP is estimated to be about 6% at 2 years and 8% at 5 years. 17 Sexual function was also evaluated in the L.I.F.T. patients. There were no reports of sexual dysfunction (erectile dysfunction and ejaculatory dysfunction) following the PUL procedure. Also, all patients were able to undergo the procedure under local anesthesia in the urologist's office. The authors attempted to standardize the number of required implants by evaluating prostate size and number of implants placed, but no correlation was found.

The methodological strengths of this study included recruitment from 19 different health centers across 3 countries, a large sample size based on a power calculation, randomized design, blinding, and comparison to a sham procedure. Analysis was also conducted using the intention-to-treat methodology and patients that experienced protocol deviations or had other prostate-related treatments were censored out of the analysis. Limitations of the L.I.F.T. RCT include the subjective nature of 4 of the 6 outcomes of interest, short follow-up of the sham group (3 months), significant losses to follow-up by year 4, and no comparison to a standard of care surgical BPH treatment (i.e. TURP).

- Sonksen et al. conducted a prospective, multi-center, randomized study to compare PUL to TURP for the treatment of LUTS secondary to BPH.[21] Currently, this is the only head-to-head comparison of PUL using the UroLift® device with the gold standard TURP procedure. Subject eligibility was based on the following criteria:
    1. ≥50 years old
    2. IPSS > 12
    3. Qmax ≤ 15 mL/s
    4. Prostate volume ≤ 60 cc per ultrasound.

  A total of n=80 participants were recruited from 10 different European health centers, randomized 1:1, and followed for 2 years. The primary study endpoint, the BPH6 questionnaire,

was specifically designed for this RCT. The BPH6 is a composite of the following 6 other validated questionnaires which assesses overall health:

1. International Prostate Symptom Score (IPSS)
2. Sexual Health Inventory for Men (SHIM)
3. Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD)
4. Incontinence Severity Index
5. Quality of Recovery Visual Analog Score
6. Clavien-Dindo classification of adverse events (AEs)

Secondary endpoints were measures of patient satisfaction, quality of life (QoL), BPH Impact Index, peak flow rate (Qmax), and sleep disturbances.

Significant improvements were seen in both groups; however, TURP was superior to PUL for improvements in IPSS and Qmax, while PUL was superior to TURP for QoL, quality of recovery, and postoperative sexual function. At the 2 year follow-up, 100% of PUL patients had preserved sexual function while 34% of TURP patients reported ejaculatory dysfunction. TURP patients also experienced a statistically significant worsening of continence function at the 2 week and 3 month follow-up (> 1 point change from baseline for the incontinence severity index (ISI) score) while the PUL patients maintained baseline continence throughout the 2 year follow-up. In regards to 2 year durability of PUL versus TURP, 6 PUL patients (13.6%) and 2 TURP patients (5.7%) required secondary treatment for return of LUTS during the follow-up period.

Strengths of this RCT included its randomized, controlled design and recruitment from 10 different health centers across Europe. Limitations are due to the small sample size, short follow-up period, and lack of blinding. A significant limitation of this RCT was the use of the BPH6 questionnaire as the primary endpoint. Although the authors stated the questionnaire is based on validated questionnaires, the BPH6 itself has yet to be validated. Using this questionnaire as the primary endpoint of the RCT creates a significant amount of doubt as to the reliability and validity of these results.

Nonrandomized Studies

- Rukstalis et al. evaluated the 2 year effectiveness and durability of PUL in a cross over study of the L.I.F.T. RCT sham patients.[22] Participants were eligible for inclusion under the criteria as the original L.I.F.T. RCT. A total of 51 patients were enrolled in the crossover study, underwent the PUL procedure, and were followed-up through 24 months. The selected outcomes of interest were IPSS, Qmax, QoL, and BPH Impact Index. The PUL procedure was efficacious for all outcomes through 24 months. Also, sexual function was preserved in all patients with no reported incidences of erectile or ejaculatory dysfunction. The reported adverse events were mild-to-moderate and typically resolved within 2 weeks. Of the 241 devices implanted in the cross over patients, 10 devices (4%) were found to have encrustation due to improper placement and required removal. Also of note, 4 patients (8%) progressed to TURP and 1 patient (2%) required additional PUL implants. Methodological strengths of this study included recruitment out of 19 health centers across 3 countries and the randomized design (from the

L.I.F.T. RCT). Limitations included the small sample size and short follow-up period. There were 15 losses to follow-up and no comparison to the gold standard surgical BPH treatment. Also, bias of the results is probable because 3 of the 4 outcome measures were subjective.

- Sievert et al. (2018) evaluated the 2 year effectiveness of Urolift among 86 patients electing the procedure instead of transurethral resection of the prostate (TURP).[23] At 2 years, 86% (n=74) of patients reported statistically significant improvement in symptoms, flow and quality of life. Some patients, 12.8% (n=11), reported persistence of LUTS or remaining PVR, only two of whom elected more implants, one of whom improved while the other did not. Adverse effects were minimal. Limitations include the relatively short follow-up period (2 years); very poor response rate at follow up (47%) and non-randomized study design. Inclusion criteria were also broader than most North American studies, with no exclusions made on the basis of high post-void residual volume (PVR), prostate size, retention history or LUTS oral therapy.

- Walsh (2017) gave an overview of advanced surgical techniques for PUL surgery.[24] Walsh noted that, "while four implants are sufficient for many prostates, there are particular anatomical variations that require additional implants. Long prostatic urethras may require three implants along the length of each lateral lobe. Patients with a high bladder neck, a modest non-obstructing median lobe or protruding anterior tissue may benefit from supplemental implant(s) near the bladder neck."

Transurethral waterjet ablation

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of transurethral waterjet ablation (e.g., Aquablation) as a treatment for benign prostatic hyperplasia. Below is a summary of the available evidence identified through September 2021.

In 2021, Hayes published a health technology assessment of Aquablation for treating BPH. The review included 7 studies, one of which was a randomized controlled trial comparing Aquablation to TURP, and 6 of which were pretest-posttest studies. Effectiveness was assessed through LUTS, QoL, medication usage, sexual function, adverse effects, and reinterventions. Urodynamic testing was used in all 7 trials,[25] finding Aquablation improved Qmax between 9.3ml/sec and 12.9ml/sec. Similarly, 6 studies investigating PVR found reduction after Aquablation treatment. The randomized trial did not statistical differences between TURP and Aquablation patients in Qmax improvement or PVR reduction. The RCT found that IPSS score was statistically noninferior to TURP at 6 months post=operation. The non-comparator studies found improvement in IPSS following Aquablation treatment. Similar results were found for QoL.

The reviewed studies had several limitations. Only one study had a comparator group, while the others were observational, non-randomized and not blinded. Sample sizes were small, follow-up was limited, and moderate attrition of patient sample. Hayes gave Aquablation a C rating, stating, "This Rating reflects a low quality body of evidence suggesting that Aquablation may improve LUTS associated with BPH at short- to intermediate-term follow-up without impact on sexual function or serious safety issues. This Rating reflects substantial uncertainty due to a lack of comparative evidence consisting of 1 study that demonstrated that Aquablation may be comparable to transurethral resection, limited long-term

evidence regarding the durability and safety of this device, and individual study quality of eligible single-arm studies."[25]

Transperineal Laser Ablation

A 2022 clinical evidence review was published by ECRI Institute on transperineal laser ablation (TPLA) for treating benign prostatic hyperplasia (BPH).[9] The review identified 4 prospective before-and-after studies and 2 retrospective before-and-after studies investigating TPLA in patients with BPH. Sample sizes ranged from 18-160 participants and follow up ranged from 1 to 12 months. International Prostate Symptom Score (IPSS) improved in every study, with 5 of 6 studies showing significant improvement. Sexual function and erectile function varied across studies, with no severe, long-term adverse effects.

ECRI determined that there are too few data on outcomes of interest to conclude efficacy of TPLA for BPH. "Studies are at a high risk of bias due to two or more of the following: retrospective design, single-center focus, and lack of control groups and randomization. Most studies are small, and none were conducted in the United States; findings may not generalize to patients in the United States. No studies compare TPLA with other minimally invasive BPH treatments or TURP. Large, multicenter RCTs are needed to validate the studies' findings and to compare TPLA with other treatments. Six ongoing trials are likely to address some evidence gaps."[9]

CLINICAL PRACTICE GUIDELINES

Water vapor thermal therapy

American Urological Association

In 2021, the American Urological Association (AUA) updated an evidence-based clinical practice guideline evaluating surgical management of LUTS attributed to BPH.[26] On the basis of grade "C" evidence, the AUA issued a moderate recommendation for water vapor thermal therapy "as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc."

A conditional recommendation was also given based on Grade C evidence level for water vapor thermal therapy as a treatment for preservation of erectile and ejaculatory function.[26]

National Institute for Health and Care Excellence (NICE)

In 2018, the NICE stated that current evidence on the safety and efficacy of transurethral water vapour ablation for urinary tract symptoms caused by benign prostatic hyperplasia is adequate to support the use of this procedure.[27]

Urethral Lift

American Urological Association (AUA)

In 2021, the AUA updated an evidence-based clinical practice guideline addressing the surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia.[28] On the basis

of grade "C" level evidence, authors issued a "moderate recommendation" supporting the use of prostatic urethral lift in patients with LUTS/BPH, a prostate volume of 30-80cc and the verified absence of an obstructive middle lobe. Authors reviewed the Rukstalis et al. study[29] because of which the FDA expanded indications to allow for patients with an obstructive median lobe. Investigators nonetheless ultimately excluded the study on the grounds that it was "essentially a case series with pre-post outcomes."[28] Authors also recommended that PUL patients be informed that symptom reduction and flow rate improvement is less significant compared to TURP, and that evidence of efficacy and retreatment rates remain "poorly defined."[26]

A "conditional recommendation" was made for PUL in patients concerned with erectile and ejaculatory function for the treatment of LUTS/BPH.

Health Evidence Review Commission (HERC) Oregon

In 2018, HERC published a coverage guidance addressing prostatic urethral lift for the treatment of benign prostatic hypertrophy.[30] On the basis of three studies, investigators issued a "strong recommendation" in support of PUL for the treatment of patients with symptomatic BPH when the following criteria are met:

- Age 50 or older
- Estimated prostate volume <80cc
- IPSS score ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure
- Failure, contraindication, or intolerance to at least three months of conventional medication therapy for benign prostatic hypertrophy

Sexual Medicine Society of North America (SMSNA)

In 2017, the SMSNA released a position statement indicating support for the UroLift® procedure as a treatment of LUTS secondary to BPH. Although this is not an evidence-based clinical practice guideline, authors recognized UroLift® as a treatment option for men with symptomatic BPH due to the available evidence supporting its, "favorable sexual side effect profile over alternative therapies."[31]

National Institute for Health and Care Excellence (NICE)

In 2021, NICE recommend the use of the UroLift® system for treating lower urinary tract symptoms caused by benign prostatic hyperplasia. Investigators recommend the UroLift® system be, "considered as an alternative to transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP). It can be done as a day-case or outpatient procedure for people aged 50 and older with a prostate volume between 30 and 80 ml."[32]

Transurethral Waterjet Ablation

American Urological Association (AUA)

In 2021, the AUA published an evidence-based clinical practice guideline addressing the surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia.[28] On the basis of grade "C" level evidence, authors issued a "conditional recommendation" or the use of robotic waterjet treatment for patients with LUTS/BPH provided prostate volume is 30-80cc.

POLICY SUMMARY

Water vapor thermal therapy

Low-quality but consistent evidence supports the use of Rezum for the treatment of benign prostatic hyperplasia. Studies to date have consistently reported positive results and low rates of adverse events. The American Urological Association and the National Institute for Health and Care Excellence both endorse water vapor thermotherapy. Results from the largest RCT conducted to date indicate significant improvements in patients' LUTS compared to baseline, although validity was limited by likely attrition bias (primary group: 32.8%, n = 44/134; cross-over group 45.3% n = 24/53). While additional, high-quality RCTs with longer term follow-up and broader inclusion criteria are required to better determine patient selection criteria, Rezum appears to be at least as safe and effective as comparable treatment options.

Urethral Lift

Although current evidence does not support the durability or efficacy of PUL compared to TURP, PUL appears to have significant advantages over TURP due to the less invasive and more convenient nature of the procedure. One of the most notable advantages of the PUL procedure is its ability to significantly preserve sexual and continence function compared to TURP. Additionally, several high-quality clinical practice guidelines conditionally recommend PUL for select patients. Due to the limited number of RCTs comparing PUL to TURP, PUL should not be seen as a replacement for TURP, but rather as an intermediate, minimally invasive option which may prolong the time to a more invasive surgical treatment. While patients typically require 4 implants, patient anatomy varies and some individuals may require additional implants to durably ensure prostatic de-obstruction. Long-term, high quality prospective studies are needed to confirm the long-term efficacy of the PUL procedure as a treatment for LUTS related to BPH.

Investigational BPH Treatments

There is insufficient evidence to support the use of transurethral waterjet ablation or transperineal laser ablation for the treatment of BPH. More high-quality comparative studies are needed to determine the benefit and safety of the treatments. Furthermore, clinical guidelines do not have strong recommendations in support of the Aquablation and no recommendations on TPLA. Therefore, transurethral waterjet ablation and transperineal laser ablation are considered investigational.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

FDA 510(k) Premarket Notifications and De Novo clearances:

Device and Company	Indications for Use	Contraindications
Rezum system by NxThera Inc.	The Rezum™ System is intended to relieve symptoms, obstructions, and reduce prostate tissue associated with BPH. It is indicated for men ≥ 50 years of age with a prostate volume 30cm3 ≤ 80cm^3. The Rezum System is also indicated for treatment of prostate with hyperplasia of the central zone and/or a median lobe. [33]	The use of the Rezūm System is contraindicated for the following: • Patients with a urinary sphincter implant • Patients who have a penile prosthesis
Urolift System by NeoTract Inc.[34]	The UroLift System is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above.	The UroLift® System should not be used if the patient has: • Prostate volume of >80 cc • An obstructive or protruding median lobe of the prostate • A urinary tract infection • Urethra conditions that may prevent insertion of delivery system into bladder • Urinary incontinence • Current gross hematuria • A known allergy to nickel

Aquabeam System by Procept BioRobotics Corporation[35]	The AQUABEAM System is intended for the resection and removal of prostate tissue in males suffering from lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia.	Do not use the Aquabeam System in patients with: • Active urinary tract or systemic infection • Known allergy to device materials • Inability to safely stop anticoagulants or antiplatelet agents perioperatively • Diagnosed or suspected cancer of the prostate
Visualase Thermal Therapy System by Biotex, Inc[36]	The Visualase Thermal Therapy System is indicated for use to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under magnetic resonance imaging (MRI) guidance in medicine and surgery in cardiovascular thoracic surgery (excluding the heart and the vessels in the pericardial sac), dermatology, ear-nose-throat surgery, gastroenterology, general surgery, gynecology, head and neck surgery, neurosurgery, plastic surgery, orthopedics, pulmonology, radiology, and urology, for wavelengths 800nm through 1064nm.	

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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