



# Medical Coverage Policy

Effective Date..... 9/15/2021  
Next Review Date..... 9/15/2022  
Coverage Policy Number ..... 0159

## Benign Prostatic Hyperplasia (BPH) Treatments

### Table of Contents

Overview .....	1
Coverage Policy.....	1
General Background.....	2
Medicare Coverage Determinations .....	19
Coding/Billing Information.....	20
References .....	21

### Related Coverage Resources

- [Botulinum Therapy](#)
- [High Intensity Focused Ultrasound \(HIFU\)](#)
- [Oral Phosphodiesterase-5 \(PDE5\) Inhibitors](#)

#### INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

### Overview

This Coverage Policy addresses surgical and minimally invasive procedures used in the treatment of benign prostatic hyperplasia (BPH).

### Coverage Policy

**Prostatic urethral lift (e.g., UroLift) is considered medically necessary for the treatment of symptomatic benign prostatic hyperplasia (BPH) when ALL of the following criteria are met:**

- age 45 years or above
- estimated prostate volume < 80 cc
- no obstructive median lobe of the prostate identified on cystoscopy
- failure, contraindication or intolerance to a trial of conventional medical therapy for BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)

**Water vapor thermal therapy (e.g., Rezūm System) is considered medically necessary for the treatment of symptomatic benign prostatic hyperplasia (BPH) when ALL of the following criteria are met:**

- age 50 years or above
- estimated prostate volume  $\geq 30 \text{ cm}^3$  and  $\leq 80 \text{ cm}^3$
- failure, contraindication or intolerance to a trial of conventional medical therapy for BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)

**Waterjet tissue ablation (e.g., AquaBeam System) is considered medically necessary for the treatment of symptomatic benign prostatic hyperplasia (BPH) when ALL of the following criteria are met:**

- age 45 years or above
- estimated prostate volume  $\geq 30 \text{ cm}^3$  and  $\leq 80 \text{ cm}^3$
- failure, contraindication or intolerance to a trial of conventional medical therapy for BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)

**The following treatments for benign prostatic hyperplasia (BPH) are considered experimental, investigational or unproven:**

- absolute ethanol injection
- cryosurgical ablation
- high-intensity focused ultrasound (HIFU)
- histotripsy
- interstitial laser coagulation (ILC)
- plasma kinetic vaporization (e.g., PlasmaKinetic™ Tissue Management System)
- prostate artery embolization
- temporary implantable nitinol device (TIND)
- transrectal thermal therapy
- transurethral balloon dilation of the prostatic urethra
- transurethral ultrasound-guided laser incision of the prostate (TULIP)
- water-induced thermotherapy (WIT)

**Note: Pharmacologic therapy is not considered within the scope of this Medical Coverage Policy. Please refer to the applicable pharmacy benefit to determine availability and the terms and conditions of coverage related to the treatment of BPH.**

## General Background

Benign prostatic hyperplasia (BPH) is a common condition caused by the abnormal growth of non-malignant prostate cells in men that can result in bothersome lower urinary tract symptoms (LUTS) (e.g., urinary urgency and frequency, weak stream and straining, urinary obstruction or retention, renal insufficiency, hydronephrosis, recurrent gross hematuria, recurrent or persistent urinary tract infections, urosepsis, large bladder diverticula, and bladder stones) (Hoffman, 2007). The most frequent indications for surgical management are moderate-to-severe voiding symptoms that are refractory to medical management.

According to a 2020 press release from the American Urological Association (AUA), “race and ethnicity are observed as significant factors associated with disparate higher incidence and poorer outcomes” for BPH. The AUA cited a retrospective cohort study in which information was collected on age, race, ethnicity, primary insurance, and rural-urban commuting area for patients presenting to Florida emergency departments with reports of lower urinary tract symptoms and acute urinary retention. The study found that men aged 45 years and older were more likely to be of non-white race, have Medicare or private insurance, and live in more urbanized areas. The authors concluded that “African-American and Hispanic patients may be untreated or undertreated for BPH in the outpatient setting”.

Treatment of BPH is individualized to the patient and involves evaluation of symptoms along with objective findings from examination and laboratory results. Initial treatment for BPH is usually drug therapy (e.g., alpha

blocker, PDE5 Inhibitor, finasteride/dutasteride) designed to relieve obstruction, but this often provides only modest relief, and up to 30% of patients require surgical intervention. There are several proposed surgical treatments for BPH that involve burning, cutting, or removal of prostatic tissue (Moul, et al., 2019; American Urological Association [AUA], last updated 2020). Transurethral resection of the prostate (TURP) is considered the gold standard for surgical treatment of BPH. However, several other minimally invasive surgical procedures and therapies have been widely used and are supported by relevant professional societies. Generally, data in the published, peer-reviewed literature demonstrate improved outcomes and support the safety and effectiveness of these other established therapies. These surgeries and therapies include:

- Contact laser ablation of the prostate (CLAP)
- Holmium laser ablation, enucleation, resection (HoLAP, HoLEP, HoLRP)
- Laser vaporization and laser ablation/coagulation)
- Open/laparoscopic prostatectomy
- Photoselective vaporization of the prostate (PVP)
- Stents (e.g., UroLume® endourethral prosthesis)
- Transurethral resection of the prostate (TURP)
- Transurethral needle ablation (TUNA), also known as radiofrequency needle ablation (RFNA)
- Transurethral electrovaporization (TUVP, TVP, TUEP), also known as transurethral vapor resection of the prostate (TUVRP)
- Transurethral microwave thermotherapy (TUMT)
- Transurethral incision of the prostate (TUIP)

### **Prostatic Urethral Lift (PUL)**

The UroLift System™ (NeoTract Inc., Pleasanton, CA) is a minimally invasive, prostatic urethral lift (PUL) system that provides anterolateral mechanical traction of the lateral lobes of the prostate, opening the urethral lumen, and reducing urinary obstruction. The delivery device contains a preloaded implant that deploys, self-adjusts, tensions, and trims a permanent tensioning suture. The suture runs from the urethra to the outer prostatic capsule and serves to compress the lateral lobe of the prostate. Implants are delivered bilaterally to separate the encroaching lobes. Four to 5 implants are typically inserted, but this varies with the size and shape of the prostate. The UroLift System is intended for the treatment of symptoms due to urinary outflow obstruction secondary to BPH in men ≥ 45 years of age. The UroLift may be used to treat prostate glands measuring <80 milliliters (mL) in size in the United States. The UroLift System is generally implanted by an urologist in an outpatient or inpatient setting. In order to determine whether a patient is an ideal candidate, the target locations and number of implants, and the ability to perform the procedure in the clinic, a planning cystoscopy and transrectal ultrasound (TRUS) are useful. The transurethral procedure to insert the UroLift is performed with the use of local or general anesthesia and oral sedation. The evidence suggests that the UroLift does not appear to compromise sexual function, which is an advantage of this device compared with the standard BPH treatment, TURP. It has been proposed that the adoption of this device for appropriately selected patients may lead to a reduction in the utilization of inpatient hospital services for more invasive procedures such as TURP (Hayes, 2020; NeoTract, 2020; Roehrborn, et al., 2016, 2015a; Perera, et al., 2015; Barkin, et al., 2012).

### **Food and Drug Administration (FDA):**

In 2013, the FDA granted a de novo classification clearance for the NeoTract® UroLift System (NeoTract, Inc., Pleasanton, CA); the system was classified as an implantable transprostatic tissue retractor system (K130651). The de novo process provides a route to market for medical devices that FDA considers to be low to moderate risk but receive class III classification because FDA has found them to be “not substantially equivalent” to any previous device that is already legally marketed. According to the FDA summary document, the UroLift system “is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to [BPH] in men age 50 and above.” The FDA contraindications state:

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

In December 2013, FDA granted 510(k) clearance for a modified version of the NeoTract UroLift System, with the prior version serving as the predicate device.

In January 2017, FDA granted 510(k) clearance for UroLift System (UL400 and UL500) for the treatment of symptoms due to urinary outflow obstruction secondary to BPH, including lateral and median lobe hyperplasia, in men 45 years of age or older. The UroLift System includes two generations of the device, the UL400 and the UL500. Both generations use the same UroLift Implant. The only differences are in the delivery device. The median lobe clinical study was the prospective Median Lobe Prostatic UroLift System Procedure (MedLift) study. The FDA contraindications were updated.

The FDA 510(k) summary states that the clinical data demonstrates that treatment of the median lobe with the UroLift System has the same safety and effectiveness as treatment of the lateral lobes (K173087). In addition, literature data and medical opinion support lowering the age indication from 50 years old to 45 years old since there is no clinical difference between the two patient populations. The overall risk profile remains the same for the UroLift System. As such, the UroLift System is substantially equivalent to the UroLift System cleared in K133281 and K172359.

The UroLift System should not be used if the patient has:

- prostate volume of >80 cc
- a urinary tract infection
- urethra conditions that may prevent insertion of delivery system into bladder
- urinary incontinence due to incompetent sphincter
- current gross hematuria

In June 2020, FDA granted 510(k) clearance for the UroLift Advanced Tissue Control (ATC) System (K200441) for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH), including lateral and median lobe hyperplasia, in men 45 years of age or older. The UroLift ATC System is substantially equivalent to the predicate UL400 device with the exception that there was a modification made to the distal tip allowing for a larger footprint during the procedure and effective mobilization of tissue when needed.

The UroLift System should not be used if the patient has:

- Prostate volume of >100 cc
- A urinary tract infection
- Urethra conditions that may prevent insertion of delivery system into bladder
- Urinary incontinence due to incompetent sphincter
- Current gross hematuria

In July 2020, FDA granted 510(k) clearance for the NeoTract UroLift 2 (UL2) System (K201837) for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH), including lateral and median lobe hyperplasia, in men 45 years of age or older. The UL2 System is substantially equivalent to the predicate UroLift UL500 System by NeoTract. Minor modifications were made to the device including the delivery handle and the implant cartridge that do not affect the overall safety and effectiveness of the UroLift procedure. Contraindications remain the same as the ATC System.

#### **Literature Review:**

Prostatic Urethral Lift (PUL) has been widely used and is supported by relevant professional societies. Evidence in the published, peer-reviewed scientific literature consists of randomized controlled trials and smaller prospective, retrospective, and case series studies. The evidence suggests that PUL using the UroLift System relieves symptoms in men age 50 years or older who have urinary outflow obstruction secondary to BPH however there is a lack of large randomized studies with long-term outcomes data comparing PUL with other established BPH treatments including TURP. Studies on the PUL procedure have been conducted in the United

States, Canada, Europe, and Australia. Patient inclusion and exclusion criteria were relatively consistent between the large trials, with patients 50 years old or older, in International Prostate Symptom Score (IPSS) greater than 12, and Qmax less than 12 to 15 mL/s. Prostate volume ranges have varied, with the US studies ranging from 30 to 80cm<sup>3</sup> and European and Australian studies typically ranging up to 100cm<sup>3</sup> (Hayes, 2020; Tanneru, et al., 2020; Jung, et al., 2019; Gratzke, et al., 2017; Rukstalis, et al., 2016, 2019; Jones, et al., 2016; Bozkurt, et al., 2016; Sønksen, et al., 2015; Perera, et al., 2015; Shore, et al., 2014; McVary, et al., 2014; Cantwell, et al., 2014; Roehrborn, et al., 2013, 2015a, 2015b, 2016, 2017a; McNicholas, et al., 2013; Chin, et al., 2012; Woo, et al., 2011, 2012).

### **Professional Societies/Organizations:**

The 2018 (revised 2020) American Urological Association (AUA) evidence-based guideline, “Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms” addresses surgical and minimally invasive procedures used in the treatment of benign prostatic hyperplasia (BPH). The AUA states that clinical scenarios exist where conservative management (e.g., medications), used alone or in combination with a minimally invasive surgery, is either inadequate or inappropriate (e.g., renal insufficiency, patient preference) in which case consideration of one of the more invasive treatment modalities is warranted. Prostatic Urethral Lift (PUL) is discussed in the updated 2018 (amended 2020) AUA evidence-based Guideline: Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms with the following statement:

- PUL may be offered as an option for patients with LUTS attributed to BPH provided prostate volume <80g and verified absence of an obstructive middle lobe.
- PUL may be offered to eligible patients who desire preservation of erectile and ejaculatory function.

### **Use Outside of the US:**

European Association of Urology (EAU) guidelines on management of non-neurogenic male LUTS include prostatic urethral lift recommendations stating to offer prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe (Strength Rating: Strong) (Gravas et al., 2021).

The updated 2018 Canadian urological Association (CUA) guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH) recommendation for PUL states: We suggest that prostatic urethral lift (Urolift) may be considered an alternative treatment for men with LUTS interested in preserving ejaculatory function, with prostates <80 cc and no middle lobe (conditional recommendation based on moderate-quality evidence) (Nickel, et al., 2018).

In a medical technologies guidance on the UroLift system for treatment of LUTS of BPH, the National Institute for Clinical Excellence (NICE) (United Kingdom) (2021) recommended that the UroLift System be considered as an alternative to transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP) in individuals who are aged 50 years or older and with a prostate volume between 30–80mL. NICE stated that the evidence supports a risk reduction in sexual function and improves quality of life.

**Water Vapor Thermal Therapy (e.g., Rezūm System):** A new approach to thermal therapy using convective radiofrequency (RF) water vapor energy has emerged to treat men with moderate-to-severe lower urinary tract symptoms (LUTS). The principles of RF-generated water vapor thermal energy are based on the thermodynamic properties of water and the use of convective versus conductive heat transfer to ablate tissue. Examples of conductive heat transfer technologies include TUNA using RF and TUMT using microwaves to generate thermal energy.

### **Food and Drug Administration (FDA):**

In August 2015, the Rezūm® System (NxThera, Inc., Maple Grove, MN) received FDA 510(k) approval (K150786). The Rezūm System is classified by the FDA as an endoscopic electrosurgical unit. The FDA indications for use state: The Rezūm 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 ≥ 30 cm<sup>3</sup> and ≤ 80 cm<sup>3</sup>. The Rezūm System is also indicated for treatment of prostate with hyperplasia of the central zone and/or median lobe. Per the FDA 510(k) Summary the device has also been tested in three clinical studies to evaluate the safety and effectiveness of the Rezūm device: 65 patients in the feasibility and pilot open label studies and in

a 197 patient randomized placebo controlled study. All of these studies showed that the device is safe and effective. The device converts water into vapor outside of the body and the vapor is delivered to the prostate tissue via a needle within the sterile delivery device. The vapor ablates the targeted tissue within the prostate via thermal ablation as energy is transferred from the vapor to the prostate tissue. The amount of vapor delivered is controlled by an RF Generator which also controls the amount of saline flush used to cool the urethra (FDA, 2015, 2016). The procedure can be performed in an office or outpatient treatment setting.

#### **Literature Review:**

Although there is a paucity of data in the peer-reviewed scientific literature comparing water vapor thermal therapy (e.g., Rezūm System) to other treatment options for BPH such as microwave TUMT and radiofrequency TUNA, the therapy has been widely used and is supported by relevant professional societies. The evidence in the peer-reviewed scientific literature provides consistent results suggesting that the Rezūm System may be an effective treatment for LUTS associated with BPH. Improvements in urinary symptoms and BPH-related quality of life from baseline were generally consistent across studies. Treatment with the Rezūm System is generally safe and not associated with loss of sexual function (Dixon, et al., 2015b, 2016; McVary, et al., 2016a; Darson, et al., 2017; Roehrborn, et al., 2017b; Hayes, 2018, annual review 2020; McVary and Roehrborn, 2018).

#### **Professional Societies/Organizations:**

Water vapor thermal therapy is discussed in the updated 2018 (amended 2020) American Urological Association (AUA) evidence-based Guideline: Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms. The recommendations were based on results of the randomized controlled trial conducted by McVary et al. (2016a). The guideline recommendation states:

- Water vapor thermal therapy may be offered to patients with LUTS attributed to BPH provided prostate volume <80g. (Conditional Recommendation; Evidence Level: Grade C)
- Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

#### **Use Outside of the US:**

The 2019 European Association of Urology (EAU) guideline on Management of Non-neurogenic Male LUTS addresses techniques under consideration including convective water vapor energy (WAVE) ablation: The Rezūm system. The guideline practical considerations state that further RCTs against a reference technique are needed to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapor energy treatment (Gravas et al., 2021).

The updated 2018 Canadian Urological Association (CUA) guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH) recommendation for convective water vapor energy ablation states that Rezūm system of convective water vapor energy ablation may be considered an alternative treatment for men with LUTS interested in preserving ejaculatory function, with prostates <80 cc, including those with median lobe (conditional recommendation based on moderate-quality evidence) (Nickel, et al., 2018).

In 2020, the National Institute for Clinical Excellence (NICE) (United Kingdom) published a medical technologies guidance on Rezūm for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. The guidance included the following recommendations:

- "Evidence supports the case for adopting Rezūm for treating LUTS caused by benign prostatic hyperplasia (BPH) in the National Health Service.
- Rezūm is a minimally invasive procedure. It should be considered as a treatment option for people with:
  - moderate to severe LUTS (International Prostate Symptoms Score [IPSS] typically 13 or over) and
  - a moderately enlarged prostate (typically between 30 cm<sup>3</sup> and 80 cm<sup>3</sup>)".

**Waterjet Tissue Ablation using the AquaBeam System:** Waterjet tissue ablation using the AquaBeam System has been proposed as the first minimally invasive medical device that allows rapid removal of prostate tissue without leaving a zone of thermal damage on the treated tissue. The AquaBeam System uses proprietary heat-free high-velocity waterjet technology for automated tissue resection as well as for optical energy delivery for

cauterization in the treatment of BPH. No heat sources are used for cutting. The AquaBeam system consists of three components: a single-use probe, a robotic hand piece, and a console. The procedure is carried out under transrectal ultrasound imaging. The AquaBeam probe is attached to the hand piece and inserted in the urethra; cystoscopic visualization is available continuously during the procedure. After mapping the desired tissue to be ablated, high-velocity sterile saline is delivered to the prostate tissue via the AquaBeam probe, which also provides a channel for aspiration of ablated tissue during the procedure. After excision of tissue from the prostate, the jet's pressure is reduced so that it can be used to carry a laser light beam to cauterize the excised area. The aim is to reduce the heat damage to adjacent tissue that is commonly seen in other available interventions.

#### **Food and Drug Administration (FDA):**

On December 21, 2017 the FDA granted a de novo classification for the AquaBeam system (PROCEPT BioRobotics Corporation, Redwood Shores, CA) (DEN170024) for the resection and removal of prostate tissue for males suffering from LUTS due to BPH. FDA clearance was supported by the international WATER randomized controlled trial (NCT02505919) comparing AquaBeam with TURP in patients with LUTS due to BPH.

On March 11<sup>th</sup>, 2021, the FDA granted 510(k) approval as a class II device for the AquaBeam Robotic System (PROCEPT BioRobotics Corporation, Redwood City, CA) for the same indication as the de novo approval that served as the predicate device. The AquaBeam system is capable of mapping the prostatic treatment area and uses a pressurized jet of fluid to cut the desired tissue.

#### **Literature Review:**

Several peer reviewed studies have been published comparing Aquablation to the gold standard of TURP. Studies consist of several randomized controlled trials including the pivotal WATER trial reporting up to three years of data, a systematic review, an open-label study, and a retrospective review. The studies are limited by small patient populations, however, no serious safety concerns have been reported. The literature demonstrates neutrality when comparing Aquablation to the hold standard of TURP and the technology is supported by relevant professional societies. The literature suggests that Aquablation may be an effective treatment option for LUTS associated with BPH in men  $\geq 45$  years old with prostate volumes between 30–80 cm<sup>3</sup> (Bach, et al., 2020; Gilling, et al., 2020; Kasraeian, et al. 2020; Gilling, et al., 2019; Hwang, et al., 2019; Pimentel, et al., 2019; Gilling, et al., 2018; Kasivisvanathan, et al., 2018; Nickel, et al., 2018; NICE, 2018; AUA, 2020; Gravas, et al., 2021).

Elterman et al. (2021) conducted a pooled meta-analysis of four international studies including one randomized controlled trial, two single-arm controlled trials, and one observational study to evaluate outcomes in men (n=425) with benign prostatic hyperplasia (BPH) and various prostate volumes who underwent Aquablation. The average age for participants across all four studies was 66.9 years old. Studies were included if they had a minimum of one year follow-up. Individual study inclusion criteria varied in regards to prostate size (i.e., 20–150mL), International Prostate Symptom Score (IPSS) (i.e.,  $\geq 12$  or diagnosed with lower urinary tract symptoms due to BPH), and Qmax (i.e., <15mL/s or diagnosed with lower urinary tract symptoms due to BPH). Individual study exclusion criteria varied as well in regards to post-void residual (i.e., >300mL, none), history of urinary retention (i.e., yes, none, only if catheter use exceeded 90 days), previous prostate surgery (i.e., yes, none), and American Society of Anesthesiologists classification (i.e., III or higher, none). Additionally, studies with less than one year follow-up were excluded. The intervention was waterjet ablation in men with prostate volumes of 20–150mL. Transurethral resection of the prostate served as the comparator in the randomized controlled trial. The primary outcome measures were IPSS, uroflowmetry, postoperative Incontinence Severity Index (ISI) and surgical retreatment. A statistically significant improvement of 16 points was noted at one year in IPSS scores. Qmax improved by 9.4mL at one year. Post-void residual urine volumes improved at one year by 42–68% depending on baseline PVR. Surgical re-treatment occurred in 0.7% of patients. All improvements were independent of prostate size and the presence or absence of a median lobe. Author noted limitations include the fact that data past one year was not available in all studies, heterogeneity of inclusion and exclusion criteria between studies. An additional limitation of the study is the small patient population.

In 2020, Gilling et al. reported on the three year results of the WATER study which was a prospective, double-blinded, multicenter, international, randomized controlled trial to compare efficacy and safety outcomes between the gold standard of transurethral resection of the prostate (TURP) to Aquablation in men with lower urinary tract

symptoms (LUTS) attributed to benign prostatic hypertrophy (BPH). Three year follow-up data was obtained on 97 Aquablation patients and 55 TURP patients. Reductions in mean International Prostate Symptom Scores (IPSS) were maintained at three years in both the Aquablation and TURP groups. There was not a significant difference in scores between groups with the exception of men with prostates  $\geq 50$  cc who averaged 3.5 points higher in the IPSS test in the Aquablation group compared to the TURP group ( $p=0.0125$ ). Quality of life scores were also similar across groups at three years ( $p=0.7845$ ). A statistically significant reduction in mean ejaculatory function scores were noted in the TURP group compared to the Aquablation group ( $p=0.0008$ ). There were no statistically significant differences between groups for erectile function. In both groups, maximum urinary flow rates increased and post-void residual and PSA decreased over the course of three years. These results were maintained at three years but did not show a statistically significant difference between groups as was the case for post-void residual and PSA as well. Adverse events were similar across both groups with the exception of anejaculation which was statistically significantly reduced in the Aquablation group ( $p=0.0039$ ). One patient in the Aquablation group and four patients in the TURP group experienced a urethral stricture ( $p=0.0567$ ). Retreatment rates were 4.3% in the Aquablation group and 1.5% in the TURP group ( $p=0.4219$ ) at three years. An author noted limitation of the study is the inability to generalize data to men with prostates larger than 80 cc.

Bach et al. (2020) conducted a prospective, multicenter, single-arm, open-label, international clinical trial to assess the safety and effectiveness of waterjet-based prostate resection (Aquablation procedure) for the treatment of benign prostatic hyperplasia (BPH). A total of 178 men with a mean age of 67.7 years were included in the study. Thirty men were lost to follow-up. Men were included in the study if they had a diagnosis of lower urinary tract symptoms (LUTS) attributable to BPH and had a prostate size of 20–150 cc. Men were excluded if they: had a bleeding disorder or were unable to stop anticoagulants or antiplatelet agents perioperatively, had a history of gross hematuria, were on systemic immune suppressants, had a contraindication to general and spinal anesthesia, were unwilling to accept a transfusion if needed, or if they had a severe illness that could prevent complete follow-up. All patients underwent the aquablation procedure by a trained surgeon. The change in International Prostate Symptom Score (IPSS) from baseline to three months served as the primary outcome measure. Secondary outcomes measured as a comparison between baseline and three months follow-up included: the proportion of patients who experienced ejaculatory or erectile dysfunction, maximal flow rate ( $Q_{max}$ ), prostate specific antigen (PSA) level, post-void residual (PVR), total Male Sexual Health Questionnaire (MSHQ) score, International Index of Erectile Function (IIEF-15) score, and subjective reporting of dysuria on a 0–5 scale. Follow-up occurred at three and 12 months. IPSS scores improved significantly by 14.5 points at three months follow-up compared to baseline ( $p<0.0001$ ) and 15.3 points at 12 months follow-up ( $p<0.0001$ ).  $Q_{max}$  significantly improved from 9.9 cc/sec at baseline to 20.3 cc/sec at three months and 20.8 cc/sec at 12 months ( $p<0.0001$ ). PVR significantly improved from 108 cc at baseline to 47 cc at three months and 61 cc at 12 months ( $p<0.0001$ ). Significant reductions in mean prostate size were noted at three months follow-up compared to baseline (35 cc vs. 59 cc;  $p<0.0001$ ). Significant improvements in MSHQ scores were not reported. Reports of dysuria significantly decreased at three month follow-up (29%) compared to baseline (51%) ( $p<0.0001$ ). Five patients ( $n=2.7\%$ ) underwent transfusion in the first week after the procedure, 14 ( $n=7.9\%$ ) returned to the operating room for post-procedure bleeding, one patient returned to the operating room for clot evacuation, one patient had a rectal perforation requiring a temporary colostomy, three patients had a meatal stenosis or stricture requiring a procedure, 15 patients ( $n=8\%$ ) experienced ejaculatory dysfunction, and one patient experienced erectile dysfunction. Author noted limitations of the study included the lack of a comparator and short-term follow-up. Additional limitations of the study include the small sample size and non-blinded design of the study.

Kasraeian et al. (2020) conducted an all-comers, single-center retrospective review of prospectively collected data to assess the safety and efficacy of robotically guided waterjet-based prostate resection in patients with lower urinary tract symptoms associated with BPH. Patients ( $n=55$ ) ranged in age from 50–84 years and had a mean prostate volume of 100cc. Patients were excluded if they were unable to stop anticoagulation prior to surgery. Patients underwent Aquablation using the AquaBeam Robotic System. Outcome measures included: operative time, preoperative to postoperative change in hemoglobin, length of hospital stay, BPH symptom score, post-void residual measurements, and sexual function. Follow-up occurred at three months. Significant improvements were noted in IPSS ( $p<0.0001$ ), quality of life ( $p<0.0001$ ), and maximum urinary flow rate ( $p=0.0001$ ). Adverse events included: hematuria ( $n=5$ ), bladder spasms ( $n=1$ ), dehydration ( $n=1$ ), intolerance of Foley catheter ( $n=1$ ), and temporarily elevated creatinine ( $n=1$ ). Limitations of the study include the small sample size, lack of a comparator, and short-term follow-up.



Desai et al. (2020) conducted a prospective, multicenter, single-arm study, known as the WATER II trial, to assess the safety and efficacy of the Aquablation procedure in men with lower urinary tract symptoms associated with BPH and with prostate volumes of 80–150 cc. Men (n=101) aged 45-80 years were included if they had: a prostate volume of 80–150 cc, a baseline International Prostate Symptom Scores (IPSS) of  $\geq 12$ , a maximum urinary flow rate (Qmax) of  $< 15$  mL/sec, a serum creatinine of  $< 2$  mg/dL, a history of failure of medical management, and a capacity to participate. Exclusion criteria were: body mass index  $\geq 42$  kg/m<sup>2</sup>, history of prostate or bladder cancer, significant bladder calculus or diverticulum, active infection, previous urinary tract surgery, urinary catheter use for 90 or more days, chronic pelvic pain, urethral stricture, meatal stenosis, use of anticholinergic agents, and any condition that would prevent follow-up. Aquablation was performed in all patients using the AquaBeam Robotic System. The following assessments were taken at baseline: IPSS, Incontinence Severity Index, Pain Intensity Scale, International Index of Erectile Function (IIEF-15), the Male Sexual Health Questionnaire (MSHQ-EjD), uroflometry, serum prostate-specific antigen (PSA), transrectal ultrasound prostate size, Qmax, and post-void residual (PVR). Two year follow-up included assessment of IPSS and uroflowmetry. PSA follow-up occurred at six, 12, and 24 months. Transrectal ultrasound prostate size follow-up occurred at three months post-operatively. Fifteen patients were lost to the two year follow-up. Mean IPSS scores showed statistically significant improvement from a baseline of 23.2 to 5.8 at two years ( $p < 0.0001$ ) regardless of prostate size. Quality of life scores showed a significant improvement of 3.4 points at two year follow-up ( $p < 0.0001$ ). Qmax significantly improved by 9.7 cc/ sec at two years ( $p < 0.0001$ ). PVR volume decreased from 131 cc at baseline to 45 cc at two years. PSA decreased from a baseline of 7.1 to 4.9 at two years while men with a PSA of  $\geq 4$  at baseline observed a significant 38% reduction at two years ( $p < 0.0001$ ). Two patients required surgical retreatment with TURP and HOLEP. An author noted limitation of the study was the lack of a comparator. Additional limitations of the study include the small patient population and the predominantly white (87.1%) make-up of the patient population compared to Asian (5%), Black (5.9%), and other (2%). Additional high quality studies are needed to evaluate the safety and efficacy of Aquablation in patients with larger prostate volumes.

Gilling et al. (2019) reported one year safety and efficacy outcomes for the WATER study. BPH symptom score improvements were similar across groups with 12-month reduction of 15.1 points after TURP or Aquablation. In both groups, mean maximum urinary flow rates increased markedly postoperatively, with mean improvements of 10.3 cc/s for Aquablation versus 10.6 cc/s for TURP ( $p = 0.8632$ ). At one year, Prostate-specific antigen (PSA) was reduced significantly ( $p < 0.01$ ) in both groups by one point; the reduction was similar across groups ( $p = 0.9125$ ). Surgical retreatment for BPH rates for TURP were 1.5% and Aquablation 2.6% within one year from the study procedure ( $p = \text{not significant [NS]}$ ). The rate of late complications was low, with no procedure-related adverse events after six months. The authors concluded that Aquablation for LUTS due to BPH provides sustained, 12-month, symptom-reduction efficacy with a low rate of late adverse events in men with prostates between 30 and 80 cc.

In a blinded, prospective, randomized multicenter study, Pimentel et al. (2019) compared urodynamic outcomes between aquablation vs transurethral resection of the prostate (TURP). Patients (n=66) were randomized 2:1 (aquablation [n=43]: TURP [n=23]) in the Waterjet Ablation Therapy for Endoscopic Resection (WATER) of prostate tissue study. Of 17 participating trial sites, seven centers performed urodynamic studies preoperatively and at a month after treatment. Urodynamic studies were optional; study centers that routinely performed urodynamic studies in clinical practice included these assessments in the trial. The primary urodynamic outcome measures were detrusor pressure at maximal flow rates (pDet@Qmax) and mean change in the Bladder Outlet Obstruction Index (BOOI). Urodynamics were measured at baseline and six months. At mean baseline pDet@qmax was 71 and 73cm H<sub>2</sub>O in the aquablation and TURP groups, respectively. At six-month follow-up, pDet@qmax decreased by 35 and 34cm H<sub>2</sub>O, respectively. A large negative shift in bladder outlet obstruction index was observed, consistent with a large reduction in the proportion of subjects with obstruction at follow-up compared to baseline (79% to 22% in aquablation and 96% to 22% in TURP). The authors concluded that in this trial, improvements after aquablation in objective measures of bladder outlet obstruction were similar to those observed after TURP. Reported limitations include that urodynamics were optional in the WATER study. This analysis had limited subjects at the seven sites performing such evaluations in the trial, which could have introduced a bias. While sample size was large enough to detect statistically significant and clinically important changes from baseline in each group, it is possible that smaller differences in urodynamic responses across treatment groups might not be detectable due to limited sample size.

In a double-blind, multicenter, prospective, randomized, controlled trial of the WATER (Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue) trial (n=181), Gilling et al. (2018) reported on individuals with moderate to severe lower urinary tract symptoms related to BPH who underwent the gold standard transurethral prostate resection (n=116) or Aquablation (n=65). The primary efficacy end point was the reduction in International Prostate Symptom Score (IPSS) at six months. The primary safety end point was the development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications. The study included men 45-80 years old with a prostate between 30-80 gm as measured by transrectal ultrasound, moderate to severe symptoms as indicated by IPSS 12 or greater and a maximum urinary flow rate less than 15 ml per second. Men were excluded from analysis if they had a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, a damaged external urinary sphincter, stress urinary incontinence, post-void residual urine greater than 300 ml or urinary retention, self-catheterization use or prior prostate surgery. Men receiving anticoagulants or bladder anticholinergics and those with severe cardiovascular disease were also excluded. Mean total operative time was similar for Aquablation and transurethral prostate resection (33 vs 36 minutes, p=0.2752) but resection time was lower for Aquablation (4 vs 27 minutes, p<0.0001). Mean IPSS had decreased from baseline by 16.9 points for Aquablation and 15.1 points for TURP. The mean difference in the change score at six months was 1.8 points greater for Aquablation (noninferiority p<0.0001 and superiority p=0.1347). At six months 100% of Aquablation vs 98% of TURP cases showed IPSS improvement. Of the patients who underwent Aquablation and transurethral prostate resection 26% and 42%, respectively, experienced a three month primary safety end point, which met the study primary noninferiority safety hypothesis and subsequently demonstrated superiority (p=0.0149). Among sexually active men the rate of anejaculation was lower in those treated with Aquablation (10% vs 36%, p=0.0003). In men with a prostate greater than 50 ml, the rate of persistent grade 1 events was (2% vs 26%, p=0.0003), the rate of persistent grade 1 events was substantially lower (2% vs 26%, p=0.0003) and the rate of Clavien-Dindo grade 2 and greater events trended in favor of Aquablation (19% vs 29%, p=0.3146). Each group achieved significant symptom relief compared to baseline with similar rates of Clavien-Dindo 2 or greater complications. The risk of anejaculation was lower with Aquablation. Larger prostates (50 to 80 ml) demonstrated a more pronounced safety and efficacy benefit. This study was limited by the short-term six month follow-up (ClinicalTrials.org: NCT02505919).

In a cohort study (n=90), Kasivisvanathan et al. (2018) reported the efficacy and safety at one year for the treatment of LUTS related to benign prostatic hyperplasia (BPH) in the United States cohort from the WATER study. Sixty individuals were treated with Aquablation and 30 were treated with TURP. A total of 87 individuals completed one year follow-up. The efficacy objective was reduction in IPSS. The safety objective was the occurrence of Clavien-Dindo persistent grade 1 or grade 2 or higher operative complications. Change in IPSS at one year between Aquablation and TURP was similar (14.5 vs 13.8, respectively, p=0.7117). The number of subjects experiencing persistent Clavien-Dindo grade 1 or Clavien-Dindo grade 2 or higher adverse events was lower in the Aquablation group compared to the TURP group (20% vs 47% respectively, p=0.0132). Amongst sexually active subjects, the rate of an ejaculation was lower in patients treated with Aquablation than TURP (9% vs 45%, respectively, p=0.0006). The authors reported that further follow-up is needed to assess the durability of Aquablation. This study is limited by small sample size and short-term follow-up.

A 2019 Cochrane Systematic Review on Aquablation of the prostate for the treatment of LUTS in men with BPH included one RCT with 184 participants comparing Aquablation to TURP (Gilling, et al., 2018). The authors did not find other prospective, comparative studies comparing Aquablation to TURP or other procedures such as laser ablation, enucleation, or other minimally invasive therapies. The conclusions state that based on short-term 12 month follow-up, the effect of Aquablation on urological symptoms is probably similar to that of TURP (moderate-certainty evidence). The effect on quality of life may also be similar (low-certainty evidence). There is uncertainty whether patients undergoing Aquablation are at higher or lower risk for major adverse events (very low-certainty evidence) signalling major uncertainty about the true effect size. Reported adverse events include postoperative pain, hematuria, urinary tract infections, urethral stricture disease, acute urinary retention and one instance of blood transfusion (Gilling, et al., 2018). The reported rates of reoperations is 2.5% (Gilling, et al., 2018). The authors are very uncertain whether Aquablation may result in little to no difference in erectile function but offer a small improvement in preservation of ejaculatory function (both very low-certainty evidence). The conclusions are based on a single study of men with a prostate volume up to 80 mL in size. Longer-term data

and comparisons with other modalities appear critical to a more thorough assessment of the role of Aquablation for the treatment of LUTS in men with BPH (Hwang, et al., 2019).

#### **Professional Societies/Organizations:**

Aquablation is discussed in the 2020 amended American Urological Association (AUA) evidence-based Guideline: Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms. One low risk of bias randomized controlled trial (n=181) assessing Aquablation was evaluated by the panel. The guideline recommendation states: Aquablation may be offered to patients with LUTS attributed to BPH provided prostate volume >30/<80g. (Conditional Recommendation; Evidence Level: Grade C) (AUA, 2020).

#### **Use Outside of the US:**

The updated 2018 Canadian Urological Association (CUA) guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH) recommends that aquablation be offered to men with LUTS interested in preserving ejaculatory function, with prostates <80 cc, with or without middle lobe. (Conditional recommendation based on moderate quality evidence). (Nickel, et al., 2018).

In a guideline on the management of non-neurogenic male LUTS, the European Association of Urology (EAU) provides a weak recommendation, despite the technology still being under investigation, for the use of aquablation in patients with “moderate-to-severe LUTS and a prostate volume of 30-80mL”. The EAU adds that patients should be informed about the risk of bleeding and lack of long-term follow-up data (Gravas et al., 2021).

In an interventional procedures guidance on transurethral water jet ablation (aquablation) for lower urinary tract symptoms caused by benign prostatic hyperplasia, the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2018) stated that this procedure raises no major safety concerns; however, the evidence on this procedure is limited in quality. NICE encourages further, quality research on this procedure.

#### **Additional Therapies:**

Numerous other therapies have been proposed for the treatment of BPH however, to date there is insufficient evidence in the published peer-reviewed scientific literature to demonstrate safety and effectiveness of these therapies.

**Absolute Ethanol Injection:** Absolute Ethanol Injection is a minimally invasive procedure that can be performed in an outpatient setting and has been proposed as a treatment for benign prostatic hypertrophy (BPH). Ethanol injection is performed using dehydrated ethanol injected with a flexible injection needle through the side channel of a cystoscope and into the targeted tissue. The result is coagulation necrosis (chemoablation) aimed at destroying the enlarged tissue (Sakr, et al., 2009).

#### **Literature Review:**

Randomized controlled trials data are lacking regarding the safety and effectiveness of absolute ethanol injection compared to standard therapy for the treatment of BPH. Two small prospective nonrandomized studies without comparators and a case series study totaling 123 patients demonstrated improvements in International Prostate Symptom Score (IPSS), quality of life scores, and significant differences in peak flow volumes and post void residual after therapy (Arslan, et al., 2014; Sakr, et al., 2009; Magno, et al., 2008).

#### **Use Outside of the US:**

The National Institute for Clinical Excellence (NICE) (United Kingdom) (NICE, 2010, updated 2015) does not recommend absolute ethanol injection for the treatment of BPH. Absolute ethanol injection for the treatment of BPH is not discussed in published guidelines of the AUA, CUA and EUA (Nickel, et al., 2018; Gravas et al., 2021).

**Cryosurgical Ablation:** Cryosurgical ablation is a minimally invasive therapy that aims to destroy prostate tissue through local freezing and has been proposed for the treatment of benign prostatic hypertrophy.

#### **Food and Drug Administration (FDA):**

The Visual-ICE Cryoablation System (Galil Medical Inc., Arden Hills, MN) was granted FDA approval through the 510(k) process (K113860) on March 12<sup>th</sup>, 2012 for the indication of cryoablative tissue destruction and can be

useful in numerous surgical procedures including prostate tissue destruction for the treatment of benign prostatic hypertrophy. The system is computer controlled and utilizes compressed argon gas that circulates through closed tipped needles to achieve tissue freezing (FDA, 2021).

**Literature Review:**

There are scarce data in the published peer-reviewed scientific literature to support the safety and effectiveness of cryosurgical ablation for the treatment of BPH. At this time the role of this therapy has not yet been established.

**High-Intensity Focused Ultrasound (HIFU):** High-intensity focused ultrasound (HIFU) is a procedure which uses a small probe to produce bursts of ultrasound that creates coagulation necrosis in a specific area of tissue. Frequencies range from 4–10 MHz, although 4 MHz is most frequently used. HIFU devices use imaging ultrasound for treatment planning and monitoring, and they deliver targeted high-intensity ultrasound that rapidly elevates the temperature in a precise focal zone. The increased tissue temperature is designed to kill excess prostate tissue (in the case of BPH). The same probe can be used for imaging, which allows both diagnostic and therapeutic testing at the same time.

**Literature Review:**

There are scarce data in the published peer-reviewed scientific literature regarding the safety and effectiveness of HIFU for the treatment of BPH.

**Use Outside of the US:**

The National Institute for Clinical Excellence (NICE) (United Kingdom) (NICE, 2015) does not recommend HIFU as an appropriate treatment for benign prostatic hyperplasia (BPH). At this time the role of high-intensity focused ultrasound for the treatment of BPH has not been established.

**Histotripsy:** Histotripsy is an extracorporeal ultrasound technology that has been proposed to treat BPH. Histotripsy is a form of focused ultrasound therapy that utilizes cavitation mechanisms to produce tissue necrosis in prostatic tissue.

**Literature Review:**

There are scarce data in the published peer-reviewed scientific literature to support the safety and effectiveness of histotripsy for the treatment of BPH. At this time the role of this therapy has not yet been established (Schuster et al., 2018; Lusuardi, et al., 2013; Hempel, et al., 2011).

**Interstitial Laser Coagulation (ILC):** ILC of the prostate by the transurethral route has been attempted using several laser and delivery devices. The laser enters the prostate and tissue is coagulated. Intraprostatic lesions reabsorb and the tissue atrophies. Consequently, some volume reduction occurs (AUA, 2010/2014).

**U.S. Food and Drug Administration (FDA):**

The Indigo® OPTIMA Laser System (Ethicon Endo-Surgery, Inc., Cincinnati, OH) was noted by the FDA (December, 2001) to be substantially equivalent to the Indigo LaserOptic Treatment System which received FDA clearance in December, 1997. It is intended to be used in the non-contact mode to photocoagulate, vaporize/ablate soft tissue (muscle, connective tissue, organ) and for cutting, incision, excision, and for coagulation in the contact mode for open/closed surgical procedures. The Diffuser Tip Fiberoptic is intended for ILC treatment of BPH.

**Literature Review:**

Indigo 830e has been studied in the United States; however, its role in treating lower urinary tract symptoms has yet to be defined. The lack of randomized controlled studies comparing ILC to other approaches has resulted in no consensus on the ILC technique.

Ng et al. (2005) conducted a study to evaluate the impact of improvements in surgical techniques and patient selection of overall outcomes of ILC of the prostate. Over a four-year period, 66 patients underwent interstitial coagulation (ILC) using the Indigo 830e. They were stratified into two groups: group one consisted of those treated during the first two years (n=47) and those treated during the latest two years (n=19) were labeled as

group two. At 12 months, maximum flow rates improved by 47% in group one and 85% in group two. Subjective measures were significantly improved from baseline in both groups but did not differ between groups. The incidence of adverse events was similar in the two groups. In a prospective study of 49 men with symptomatic benign prostatic hyperplasia (BPH) who underwent ILC, Daehlin et al. (2007) reported a decrease in International Prostate Symptom Scores (IPSS), and an increase in peak urinary flow; however, twenty-two patients (50%) required retreatment.

At present there is insufficient evidence in the published peer-reviewed scientific literature to support the effectiveness of interstitial laser coagulation (ILC); its role in the treatment of benign prostatic hyperplasia (BPH) has not yet been established.

**Plasma Kinetic Vaporization using the PlasmaKinetic™ Tissue Management System:** The PlasmaKinetic™ Tissue Management System (Gyrus ACMI, Southborough, MA) uses plasma energy to vaporize tissue with minimal thermal spread and enhanced hemostasis.

#### **U.S. Food and Drug Administration (FDA):**

In July 2003, the PlasmaKinetic Superpulse System (Gyrus, Maple Grove, MN) received 510(k) premarket notification that the device is substantially equivalent to predicate devices and is safe and effective in its intended use. It is intended for use for ablation, removal, resection and coagulation of soft tissue and where associated hemostasis is required. Predicate devices are the PlasmaKinetic Generator, the PlasmaKinetic Endourology Generator, and the Endourology Axiopolar Resectoscope Electrode.

#### **Literature Review:**

There are scarce data in the published, peer-reviewed scientific literature regarding the safety or effectiveness of this therapy and its role in the treatment of BPH has not yet been established.

**Prostate Artery Embolization:** Prostatic arterial embolization (PAE) is proposed as a minimally invasive procedure and as an alternative to transurethral resection of the prostate (TURP) or open prostatectomy for the treatment of benign prostatic hypertrophy (BPH). PAE for BPH has been proposed to reduce the blood supply of the prostate gland, causing some of it to undergo necrosis with subsequent shrinkage. The procedure is performed under local anesthesia and sedation using a percutaneous transfemoral approach by an interventional radiologist, in consultation with the urologist. The arterial occlusion may be achieved through the use of polyvinyl alcohol particles, coil embolizers, or microspheres (Hayes, 2019, annual review 2020).

#### **Literature Review:**

Short and limited mid-term data in the published, peer-reviewed literature demonstrate improved outcomes of PAE as a minimally invasive procedure for the treatment of BPH. Additional large, well-designed studies with longer follow-up are needed to validate results (Hayes, 2019, annual review 2020; Jiang et al., 2019; Zumstein, et al., 2018; Carnevale, et al., 2017; Kuang et al, 2017; Pyo et al., 2017; Wang et al, 2016; de Assisi, et al., 2015; Wang, et al., 2015; Russo, et al., 2015; Gao, et al., 2014; Bagla, et al., 2014; Pisco, et al., 2013).

Insausti et al. (2020) conducted a non-inferiority randomized controlled trial (n=45) to assess the efficacy and safety of prostate artery embolization (PAE) versus Transurethral Resection of the Prostate (TURP) in the treatment of lower urinary tract symptoms (LUTS) related to BPH. Patients were included if: age >60 years, TURP was indicated; the International Prostate Symptom Score (IPSS) was  $\geq 8$ , quality of life (QoL) related to LUTS was  $\geq 3$ , and the peak flow rate (Qmax) was  $\leq 10$  mL/s or urinary retention. Patients were also included if LUTS related to BPH was refractory to medical treatment for at least six months or the patient could not tolerate medical treatment. Patients were excluded if they had: advanced atherosclerosis and tortuosity of the iliac arteries, non-visualization of the prostatic artery or other accessory arteries supplying the prostate on computed tomography angiography, urethral stenosis, detrusor failure or neurogenic bladder, glomerular filtration rate of less than 30 mL/min, and the presence of prostate cancer. The intervention was PAE (n=23) performed with 300- to 500- $\mu$ m microspheres under local anesthesia. Bipolar TURP (n=22) under spinal or general anesthesia served as the comparator. Primary outcomes were changes in Qmax and IPSS score. QoL and prostate volume (PV) changes were secondary outcomes. Follow up occurred at three months, six months, and 12 months post procedure. Results showed a nonsignificant 3.31mL/second difference in Qmax in favor of TURP ( $p < 0.862$ ) and a 3.04 point difference in IPSS score in favor of PAE ( $p = 0.080$ ). A significant difference was seen in QoL in favor

of PAE ( $p=0.002$ ), and a 22.1 cm<sup>3</sup> difference in PV in favor of TURP ( $p<0.001$ ). Adverse events for TURP were urethral stricture, retrograde ejaculation, erectile dysfunction, decreased ejaculatory volume, and mild hematuria. Adverse events for PAE were rectal ischemia; radiodermatitis; urinary retention, irritation, pain, discomfort; erectile dysfunction; and transient changes in the color of the penis. Author noted limitations were: small sample size, patient attrition, non-blinding of patients, and short term follow-up.

Pisco et al. (2020) conducted an RCT ( $n=80$ ) to assess the safety and efficacy of prostatic artery embolization (PAE) compared with sham in the treatment of lower urinary tract symptoms (LUTS) caused by benign prostatic hypertrophy (BPH). Patients ranged in age from 48-76 years. Inclusion criteria were as follows: age greater than 45 years; maximum urine flow rate ( $Q_{max}$ )  $<12$  ml/s; prostate volume (PV)  $\geq 40$  cm<sup>3</sup>, and diagnosis of severe LUTS/BPH refractory to medical management. The exclusion criteria included: computed tomography (CT) angiography showing that prostatic arteries were not feasible for PAE; previous surgical or invasive prostate treatments; prostatitis or suspected prostatitis; history of prostate or bladder cancer or pelvic irradiation; active or recurrent urinary tract infections; history of neurologic condition or disease causing or impacting LUTS; advanced atherosclerosis and tortuosity of iliac and prostatic arteries; secondary renal insufficiency; large bladder diverticula or stones; detrusor failure; history of acute urinary retention; current severe, significant, or uncontrolled disease; bleeding disorder; hypersensitivity or contraindication to tamsulosin use; mental condition or disorder that would interfere with the patient's ability to provide informed consent; participation in a study of any investigational drug or device in the previous three months; and administration of the 5-ARIs finasteride and dutasteride in the previous two week and four months respectively. The intervention was PAE ( $n=40$ ) performed with 300-500  $\mu$ m microspheres. Sham PAE without embolization ( $n=40$ ) served as the comparator. After six months follow-up, the sham group also underwent PAE and were then followed for another six months. Primary outcome measures included: change from baseline International Prostate Symptom Score (IPSS) and quality of life (QoL) score. The secondary outcomes measured were changes from baseline in: the BPH Impact Index, the 15-item International Index of Erectile Function (IIEF-15), PV,  $Q_{max}$ , postvoid residual urine volume (PVR), and PSA. Follow up occurred at one, three, and six months post treatment. Statistically significant improvement was shown in IPSS ( $p<0.0001$ ) and QoL ( $p<0.0001$ ) scores at the 6- month follow up. Secondary outcome results at six months also showed statistically significant improvement with a decrease in BPH-II scores of 2.28 and 6.33 points in the sham and PAE groups respectively ( $p<0.0001$ ), a decrease in prostate volume of 0.06 cm<sup>3</sup> and 17.6 cm<sup>3</sup> in the sham and PAE groups respectively ( $p=0.002$ ), an increase in  $Q_{max}$  of 2.80 ml/s and 6.82 ml/s in the sham and PAE groups respectively ( $p=0.005$ ), an increase in PVR volume in the sham group of 8.63 ml and a decrease of 59.9 ml in the PAE group ( $p=0.03$ ), and a decrease in PSA of 0.02 ng/dl and 1.51 ng/dl in the sham and PAE groups respectively ( $p=0.01$ ). A statistically significant improvement was not shown in IIEF-15 scores with an increase of 5.95 and 9.53 points in the sham and PAE groups respectively ( $p=0.29$ ). The following adverse events were reported: perineal pain, urethral pain, dysuria, ecchymosis, hematospermia, hematuria, inguinal hematoma, expelled prostate fragment, rectorrhagia, and UTI. Author noted limitations included: inclusion of severe LUTS only, the large PVs of the participants, small sample sizes, and short term follow-up.

A 2019 (reviewed 2020) Hayes comparative effectiveness review of PAE for treatment of BPH summarized that low-quality, consistent evidence for PAE is associated with significant improvements in lower urinary tract symptoms, although improvements were significantly less robust than those associated with transurethral resection of the prostate (TURP) or open prostatectomy. The evidence suggests that PAE is associated with fewer complications than TURP or open prostatectomy. Uncertainty remains regarding optimal patient selection criteria for PAE versus TURP and the long-term safety and efficacy of PAE beyond two years. The evidence base for this report included ten studies that evaluated PAE for the treatment of BPH; five randomized controlled trials including a post hoc analysis of an RCT and five prospective or retrospective cohort studies. The 2020 Hayes annual review identified eight new relevant publications that did not change the Hayes conclusion.

In a 2019 meta-analysis, Jiang et al. evaluated studies comparing PAE to TURP and evaluated short-term outcomes with at least 12 months follow-up. Four studies were included in the review ( $n=506$ ), two randomized controlled trials (Gao, et al., 2014; Carnevale, et al., 2016) and two comparative observational studies (Qiu, et al., 2017; Ray, et al., 2018). In a pooled analysis of data from two studies, there was no significant difference in post-operative IPSS. The post-operative peak flow rate ( $Q_{max}$ ) was significantly higher in the TURP group than the PAE group. Similarly, the post-operative prostate volume and quality of life improved significantly more in the TURP group. Data from two studies found no statistically significant differences in complications in the two

groups. The authors reported that additional multi-center high quality randomized controlled trials with large sample size are needed to verify the clinical efficiency of TURP and PAE for the treatment of BPH.

Malling et al. (2019) conducted a systematic review and meta-analysis of 10 studies (randomized controlled trials and prospective studies) (n=1,046) to review the efficacy and safety of prostate artery embolization (PAE) in the treatment of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS). The number of patients in each study ranged from 22-630 and the mean age was 68.6 years. Studies evaluating the efficacy of PAE to treat BPH were included. Studies with less than ten participants, short-term follow-up (<6 months) or indications for PAE other than BPH were excluded. The intervention was PAE to treat BPH and TURP served as a comparator. The primary outcome measure was mean change in the International Prostate Symptom Score (IPSS). Secondary outcome measures were quality of life (QoL), prostate volume (PV), prostate-specific antigen (PSA), post-void residual (PVR), peak urinary flow (Qmax), International Index of Erectile function (IIEF-5), complications, and technical and clinical success rates. Follow-up for nine of the studies was 12 months while one study, with an unreported number of participants, was followed for 6.5 years. Meta-analysis showed statistically significant improvement in IIEF (p=0.005) and all other outcomes (p<0.001) at 12 months follow up. Adverse events included: transient dysuria, increased urinary frequency, post embolization syndrome, bladder ischemia, UTI, and persistent perineal pain for three months. Author noted limitations included: heterogeneity of IPSS measurement thresholds, patient selection, embolization technique, small sample sizes, short-term follow-up, and one long-term follow-up that is based on a small sample size. Additional, high quality studies are needed to support the safety and efficacy of PAE.

In a 2018 meta-analysis and systematic review, Zumstein et al. evaluated studies comparing PAE with TURP for patients with BPH. The authors included five studies (n=708); (Gao et al., 2014; Russo et al., 2015; Carnevale et al., 2016; Abt et al., 2018; Ray et al., 2018) with at least 12 month follow-up. The authors concluded that PAE was less effective than TURP and had less favorable IPSS scores, peak urinary flow, prostate volume reduction, and prostate void residual. In contrast, International Index of Erectile Function scores were better and complications were fewer for PAE versus TURP. The authors reported that additional randomized controlled trials with longer follow-up periods are needed to evaluate the mid- and long-term efficacy and safety of PAE and to assess its ideal spectrum of indications, also compared to less invasive procedures such as TUMT, TUNA, or prostatic urethral lift.

In a systematic review and meta-analysis, Wang et al. (2016) evaluated the efficacy and safety of PAE on LUTS related to BPH. Twelve prospective and retrospective studies involving 840 participants were included. Compared with baseline, the International Index of Erectile Function (IIEF-5; International Prostate Symptom Score) scores, the quality of life scores, peak urinary flow rate (Qmax) and post void residual volume all had significant improvements during the 24-month follow-up (all P<0.00001). Both prostate volume (PV) and prostate-specific antigen had significant decrease during the 12-month follow-up (p<0.00001 and p=0.005, respectively), except postoperative 24 months (p=0.47 and p=0.32, respectively). The IIEF-5 short form scores had significant increase at postoperative six months (p=0.002) and 12 months (p<0.0001), except postoperative one month (p=0.23) and 24 months (p=0.21). For large volume (PV ≥ 80 mL) BPH, the results were similar. There were no life-threatening complications. The major limitations of this study include heterogeneity in the participants chosen, different materials and sizes of embolic agents and bilateral or unilateral embolization. Additional limitation is the small sample sizes of some included studies with no long-term follow-up. Data in the studies covered by this meta-analysis are insufficient to determine whether or not PAE is as good as TURP. Similar conclusions were reported in a systematic review and meta-analysis of PAE for LUTS related to BPH by Pyo et al. (2017) and in a 2017 systematic review of PAE in the treatment of symptomatic BPH (Kuang, et al., 2017).

In a prospective series matched study (n=160), Russo et al. (2015) evaluated one-year surgical and functional results and morbidities of prostatic artery embolization (PAE) vs open prostatectomy (OP). Inclusion criteria included lower urinary tract symptoms or benign prostatic obstruction, IPSS ≥ 12, prostate-specific antigen (PSA) <4 ng/mL, or PSA between 4 and 10 ng/mL but negative prostate biopsy, total prostate volume >80 cm<sup>3</sup>, and peak flow (PF) <15 mL/s. Follow-up was performed at one month, six months, and one year. Primary end points of the study were the comparison regarding IPSS, International Index of Erectile Function-5, PF, post voidal residual (PVR), and IPSS quality of life (IPSS-QoL) after one year of follow-up. The authors reported that PAE

was inferior to OP in terms of one-year functional outcomes such as the reduction of IPSS and PVR and the increase of PF. Further clinical trials comparing PAE with other minimally invasive surgical are required.

In a prospective randomized study (n=114), Gao et al. (2014) compared prostatic arterial embolization (PAE) (n=57) and transurethral resection of the prostate (TURP) (n=57) in the care of patients with benign prostatic hyperplasia (BPH). The groups were compared regarding relevant adverse events and complications. Functional results including improvement of International Prostate Symptom Score (IPSS), quality of life (QOL), peak urinary flow, postvoiding residual urine volume, prostate-specific antigen (PSA) level, and prostate volume-were assessed at one-, three-, six-, 12-, and 24-month follow up. Overall technical success rates for TURP and PAE were 100% and 94.7%, respectively; the clinical failure rates were 3.9% and 9.4%, respectively. The six functional results showed improvements after TURP and PAE at all follow-up time points when compared with preoperative values (p=0.001). The TURP group showed greater degrees of improvement in the IPSS, QOL, peak urinary flow, and postvoiding residual urine volume at one and three months, as well as greater reductions in the PSA level and prostate volume at all follow-up time points, when compared with the PAE group (p<0.05). The PAE group showed more overall adverse events and complications (p=0.029), mostly related to acute urinary retention (25.9%), postembolization syndrome (11.1%), and treatment failures (5.3% technical; 9.4% clinical). The authors reported that “the advantages of the PAE procedure must be weighed against the potential for technical and clinical failures in a minority of patients.”

### **Professional Societies/Organizations:**

The 2020 updated American Urological Association (AUA) evidence-based guideline on the “Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms” stated that:

Artery Embolization (PAE) for the treatment of LUTS secondary to BPH is not supported by current data and trial designs, and benefit over risk remains unclear; therefore, PAE is not recommended outside the context of clinical trials.

In 2018, the Society of Interventional Radiology (SIR) updated their 2014 position statement on PAE for treatment of LUTS attributed to BPH. The updated position statement addresses the global experience with PAE stating the joint position and recommendations of SIR, the Cardiovascular and Interventional Radiological Society of Europe, Society Française de Radiologie, and the British Society of Interventional Radiology. The societies made the following recommendations for PAE (McWilliams, et al., 2018):

- PAE is an acceptable minimally invasive treatment option for appropriately selected men with BPH and moderate to severe LUTS. (Level of evidence: B; strength of recommendation: strong.)
- PAE can be considered as a treatment option in patients with BPH and moderate to severe LUTS who have very large prostate glands (> 80 cm<sup>3</sup>), without an upper limit of prostate size. (Level of evidence: C; strength of recommendation: moderate.)
- PAE can be considered as a treatment option in patients with BPH and acute or chronic urinary retention in the setting of preserved bladder function as a method of achieving catheter independence. (Level of evidence: C; strength of recommendation: moderate.)
- PAE can be considered as a treatment option in patients with BPH and moderate to severe LUTS who wish to preserve erectile and/or ejaculatory function. (Level of evidence: C; strength of recommendation: weak.)
- PAE can be considered in patients with hematuria of prostatic origin as a method of achieving cessation of bleeding. (Level of evidence: D; strength of recommendation: strong.)
- PAE can be considered as a treatment option in patients with BPH and moderate to severe LUTS who are deemed not to be surgical candidates for any of the following reasons: advanced age, multiple comorbidities, coagulopathy, or inability to stop anticoagulation or antiplatelet therapy. (Level of evidence: E; strength of recommendation: moderate.)
- PAE should be included in the individualized patient-centered discussion regarding treatment options for BPH with LUTS. (Level of evidence: E; strength of recommendation: strong.)
- Interventional radiologists, given their knowledge of arterial anatomy, advanced microcatheter techniques, and expertise in embolization procedures, are the specialists best suited for the performance of PAE. (Level of evidence: E; strength of recommendation: strong.)



**Use Outside of the US:**

The updated 2018 Canadian Urological Association (CUA) guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH) recommendation for PAE states that PAE should not be offered at this time for the treatment of LUTS due to BPH (conditional recommendation based on moderate-quality evidence). The guideline authors note that PAE performed by interventional radiologists, at specialized centers, is associated with significant clinical improvements from baseline to one year. However, outcomes are inferior compared with TURP and open simple prostatectomy. Further, non-targeted embolization is associated with ischemic complications (e.g., bladder ischemia, transient ischemic proctitis, urethral and ureteral stricture, or seminal vesicles ischemia) (Nickel, et al., 2018).

In a guideline on the management of non-neurogenic male LUTS, the European Association of Urology (EAU) offers a weak recommendation for prostatic arterial embolization in individuals who would like a minimally invasive treatment option and have been made aware that outcomes are less optimal than TURP. Additionally, the EAU points out that this treatment option remains under investigation and should only be offered in facilities where the urologist is working collaboratively with a trained interventional radiologist (Gravas et al., 2021).

In 2018, the National Institute for Clinical Excellence (NICE) (United Kingdom) published an Interventional Procedure Guidance Prostate Artery Embolisation for Lower Urinary Tract Symptoms caused by benign prostatic hyperplasia which includes the following recommendations:

- “Current evidence on the safety and efficacy of prostate artery embolisation for benign prostatic hyperplasia is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance consent and audit.
- Patient selection should be done by a urologist and an interventional radiologist.
- This technically demanding procedure should only be done by an interventional radiologist with specific training and expertise in prostatic artery embolization”.

**Temporary implantable nitinol device (TIND):** A TIND is a device proposed to provide a minimally invasive means of increasing prostatic urethral patency to relieve the symptoms of urinary outflow obstruction secondary to benign prostatic hypertrophy (BPH). The TIND is crimped and delivered through a cystoscope sheath, and then, when placed in the urethra, it is released from the cystoscope sheath to assume its expanded configuration, thereby reshaping the urethra and the bladder neck. It is removed after a few days under local anesthesia. (Magistro, et al., 2018; 2018; Marcon, et al., 2018; Nickels, et al., 2018; Porpiglia, et al., 2015).

**Food and Drug Administration (FDA):**

In 2020, the FDA granted a de novo classification clearance (DEN190020) for the iTind System (Medi-Tate Ltd, Or Akiva, IL). The system was classified as a temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia. According to the FDA summary document, the iTind System “is intended for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above.” The self-expanding implant is deployed at the bladder neck between the obstructed prostatic lobes by means of a pre-mounted device on a dedicated guide wire. The implant provides continuous pressure for 5–7 days and is removed using a Foley catheter (FDA, 2020).

**Literature Review:**

There are scarce data in the published peer-reviewed scientific evidence to determine the safety and efficacy of the TIND as a treatment option for BPH.

Porpiglia et al. (2019) conducted a prospective single-arm, multicenter study (n=81) to assess the feasibility, safety and efficacy of a second-generation of temporary implantable nitinol device (iTIND; Medi-Tate Ltd, Or-Akiva, Israel) for the treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). The mean age of participants was 65 years. The inclusion criteria were: LUTS, International Prostate Symptom Score (IPSS)  $\geq 10$ , maximum urinary flow rate (Q<sub>max</sub>)  $\leq 12$  mL/s, and prostate volume  $< 75$  mL. The exclusion criteria were: hemostatic disorders, neurogenic bladder and/or sphincter abnormalities, impaired renal function, history of urethral strictures, post-void residual urine volume (PVR)  $> 250$  mL, urinary bladder stones, bladder cancer, obstructive median lobe, active UTI, and previous prostate surgery. After discontinuation of

pharmacological therapy, patients underwent implantation of the iTIND within the bladder neck and the prostatic urethra under light sedation. The device was removed five to seven days later. There were no comparators in this single arm study. The outcome measures were maximum urinary flow rate (Q<sub>max</sub>), International Prostate Symptom Score (IPSS), quality of life (QoL), and post-void residual urine volume (PVR). Follow-up was conducted at one, three, six, and 12 months postoperatively. Statistical significance was shown with an improvement in Q<sub>max</sub> from a baseline of 7.3 ml/s to 11.2 ml/s at one month, 12.4 ml/s at three months, 13.69 ml/s at six months, and 14.7 ml/s at one year follow up (p<0.001); an improvement in total IPSS from a baseline of 26.22 to 13.81 at one month, 11.61 at three months, 11.57 at six months, and 10.38 at one year (p<0.001); an improvement in QoL from a baseline of 4 to two at one, three, and six months, and one at one year follow up (p<0.001); and an overall improvement in PVR from a baseline of 76.17 mL to 49.84 mL at one month, 46.75 mL at three months, 48.84 mL at six months, and 34.03 at one year follow up (p<0.001). The authors reported a 5% treatment failure rate (n=4). Adverse events included: hematuria, urinary urgency, urinary retention, pain, dysuria, and UTI. Author noted limitations of the study include: short term follow-up, lack of a control, selection bias, and patient attrition.

#### **Use Outside of the US:**

The temporary implantable nitinol device (TIND) has CE mark approval. The manufacturer website for the TIND device states the device is available in the European Union, UK, Israel, Australia, Brazil, and the USA.

In an interventional procedures guidance document for prostatic urethral temporary implant insertion for lower urinary tract symptoms (LUTS) cause by benign prostatic hyperplasia (BPH), the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2019) stated that the safety and efficacy of prostatic urethral temporary implant insertion for LUTS caused by BPH is insufficient and lacking quality. As such, further research is needed in the form of quality randomized controlled trials.

The 2018 Canadian Urological Association (CUA) guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH) recommends that TIND should not be offered at this time for the treatment of LUTS due to BPH (Nickel , et al., 2018).

**Transrectal Thermal Therapies:** There are scarce data in the published peer-reviewed scientific evidence to determine the safety and efficacy of thermal therapy via the rectum as a treatment option for BPH. At this time the role of this therapy has not yet been established.

**Transurethral Balloon Dilation of the Prostatic Urethra:** Transurethral balloon dilation of the prostatic urethra, also known as endoscopic balloon dilation of the prostatic urethra, involves the insertion of a balloon catheter through the urethra into the prostatic urethra where it is inflated to stretch the urethra where it has been narrowed by the prostate.

#### **Literature Review:**

There are scarce data regarding the safety and effectiveness of this therapy for the treatment of BPH and its role has not yet been established.

**Transurethral Ultrasound Guided Laser Incision of the Prostate (TULIP):** TULIP is a procedure that is similar to transurethral incision of the prostate except that cuts are made with a laser. Laser energy is delivered under ultrasound guidance, producing necrosis. TULIP is a difficult procedure with a very high incidence of incontinence, a delayed onset of improvement, and no ability to obtain tissue for histological examination. TULIP is rarely used by urologists because it has been surpassed by instruments that are easier to use (Fitzpatrick, 2011).

#### **Literature Review:**

There are scarce data in the published, peer-reviewed scientific literature regarding the effectiveness of TULIP and the role of this therapy in the treatment of BPH has not yet been established.

**Water-Induced Thermotherapy (WIT):** WIT is a minimally-invasive therapy that uses hot water circulating through a urethral balloon catheter to deliver heat energy to prostate tissue and thereby shrink the prostate and treat symptoms of BPH. It is generally considered only for patients who cannot undergo TURP or who require

less invasive treatments, however the long-term safety and effectiveness of this treatment in this or other proposed subsets of individuals has not been proven.

**U.S. Food and Drug Administration (FDA):**

The AquaTherm device, formerly known as the Thermoflex™ Water-Induced ThermoTherapy System (ACMI, Southborough, MA, previously Argomed, Inc., Cary, NC) is a catheter-based thermal therapy device for the treatment of symptoms due to urinary outflow obstruction secondary to BPH. FDA 510(k) class II approval was received in 1999.

**Literature Review:**

There are scarce data in randomized controlled clinical trials or comparative studies regarding outcomes of WIT as a treatment for BPH. Minardi et al. (2004) reported that WIT resulted in a reduction of prostatic volume of 5.2% compared with a decrease of 48.4% when transurethral resection of the prostate (TURP) was performed. The urine flow rate increased more after TURP (75.3%) than after WIT (16.7%). Residual prostate volume decreased more after TURP (89.8%) than after WIT (25.2%), an increase of maximum flow rate of 16.7% and a decrease of residual volume of 25.2%. The relief of bladder outlet obstruction was indicated by the decrease of detrusor pressure at maximum flow rate in comparison to baseline values; decreases of 27.5% were noted for WIT compared with decreases of 48% for transurethral resection of the prostate (TURP).

At this time there is insufficient evidence in the peer-reviewed scientific evidence to determine the safety and effectiveness of WIT for the treatment of BPH. Additionally, there is insufficient direct comparison of WIT to other treatment options for BPH; optimal protocols have not been established and long-term information regarding duration of treatment effect or adverse effects is lacking.

**Use Outside of the US:**

In a clinical guideline document on the management of LUTS, the National Institute for Clinical Excellence (United Kingdom) does not comment on the use of WIT as a treatment option for BPH (NICE, 2010, 2015).

**Medicare Coverage Determinations**

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD	National Government Services, Inc.	Water Vapor Thermal Therapy for LUTS/BPH (L37808)	11/01/2020
LCD	CGS Administrators, LLC	Laser Ablation of the Prostate (L34090)	4/1/2021
LCD	CGS Administrators, LLC	Fluid Jet System in the Treatment of Benign Prostatic Hyperplasia (BPH) (L38378)	3/25/2021
LCD	National Government Services, Inc.	Fluid Jet System in the Treatment of Benign Prostatic Hyperplasia (BPH) (L38367)	11/1/2020
LCD	First Coast Service Options, Inc.	Transurethral Waterjet Ablation of the PROSTATE (L38726)	12/27/2020
LCD	Noridian Healthcare Solutions, LLC	Transurethral Waterjet Ablation of the PROSTATE (L38705)	12/27/2020
LCD	Novitas Solutions, Inc.	Transurethral Waterjet Ablation of the PROSTATE (L38712)	12/27/2020
LCD	Palmetto GBA	Transurethral Waterjet Ablation of the PROSTATE (L38549)	12/27/2020
LCD	Wisconsin Physicians Service Insurance Corporation	Transurethral Waterjet Ablation of the PROSTATE (L38682)	12/27/2020

Note: Please review the current Medicare Policy for the most up-to-date information.

## Coding/Billing Information

- Note:** 1) This list of codes may not be all-inclusive.  
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

CPT®* Codes	Description
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)
53854	Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy
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).

HCPCS Codes	Description
C2596	Probe, image-guided, robotic, waterjet ablation
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants

**Considered Experimental/Investigational/Unproven when used to report any procedure listed in this policy as Experimental/Investigational/Unproven for the treatment of benign prostatic hyperplasia (BPH):**

CPT®* Codes	Description
37242	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, other than hemorrhage or tumor (eg, congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)
53899	Unlisted procedure, urinary system
55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance and monitoring)
55880	Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance
55899	Unlisted procedure, male genital system
76999	Unlisted ultrasound procedure (eg, diagnostic, interventional)

HCPCS Codes	Description
C9769	Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts

\*Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.

## References

1. Abt D, Hechelhammer L, Müllhaupt G, Markart S, Güsewell S, Kessler TM, et al. Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial. *BMJ*. 2018 Jun 19;361:k2338.
2. American Urological Association (AUA). Benign prostatic hyperplasia: Surgical management of benign prostatic hyperplasia/lower urinary tract symptoms. May 2018. Amended 2019. Amended 2020. Accessed Jul 27, 2021. Available at URL address: [http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-\(bph\)-guideline](http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-(bph)-guideline)
3. American Urological Association (AUA). Management of benign prostatic hyperplasia. 2003. Revised 2010. Reviewed and validity confirmed 2014. Accessed Jul 27, 2021. Available at URL address: [http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-\(bph\)-guideline/benign-prostatic-hyperplasia-\(2010-reviewed-and-validity-confirmed-2014\)](http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-(bph)-guideline/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014))
4. American Urological Association (AUA). Press releases. Studies highlight barriers to and disparities in access to care for patients with prostate disease. May 15, 2020. Accessed Jul 30, 2021. Available at URL address: <http://auanet.mediaroom.com/2020-05-15-Studies-Highlight-Barriers-to-and-Disparities-in-Access-to-Care-for-Patients-with-Prostate-Disease>
5. American Urological Association (AUA). Transurethral destruction of prostate tissue; by radio-frequency generated water thermotherapy (Rezūm<sup>®</sup>) appeal letter. Dec 5, 2019. Accessed Jul 27, 2021. Available at URL address: <http://www.auanet.org/practice-resources/coding-and-reimbursement/coding-resources-and-information/appeal-letters>
6. Arslan M, Oztürk A, Goger YE, Aslan E, Kilinc M. Primary results of transurethral prostate ethanol injection. *Int Urol Nephrol*. 2014 Sep;46(9):1709-13.
7. Aoun F, Marcelis Q, Roumeguère T. Minimally invasive devices for treating lower urinary tract symptoms in benign prostate hyperplasia: technology update. *Res Rep Urol*. 2015 Aug 19;7:125-36.
8. Bagla S, Martin CP, van Breda A, Sheridan MJ, Sterling KM, Papadouris D, et al. Early results from a United States trial of prostatic artery embolization in the treatment of benign prostatic hyperplasia. *J Vasc Interv Radiol*. 2014 Jan;25(1):47-52.
9. Barkin J, Giddens J, Incze P, Casey R, Richardson S, Gange S. UroLift system for relief of prostate obstruction under local anesthesia. *Can J Urol*. 2012 Apr;19(2):6217-22.
10. Bouza C, Lopez T, Magro A, Navalpotro L, Amate JM. Systematic review and meta-analysis of Transurethral Needle Ablation in symptomatic Benign Prostatic Hyperplasia. *BMC Urol*. 2006 Jun21;6(1):14
11. Boyle P, Robertson C, Vaughan ED, Fitzpatrick JM. A meta-analysis of trials of transurethral needle ablation for treating symptomatic benign prostatic hyperplasia. *BJU Int*. 2004 Jul;94(1):83-8.
12. Bozkurt A, Karabakan M, Keskin E, Hirik E, Balci MB, Nuhoglu B. Prostatic Urethral Lift: A New Minimally Invasive Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *Urol Int*. 2016;96(2):202-6.
13. Burke N, Whelan JP, Goeree L, Hopkins RB, Campbell K, Goeree R, et al. Systematic review and meta-analysis of transurethral resection of the prostate versus minimally invasive procedures for the treatment of benign prostatic obstruction. *Urology*. 2010 May;75(5):1015-22.

14. Burr JM, Hay DJ, Ludgate S, Abrams P. Hot and cold technologies for tissue ablation in urology. *BJU Int.* 2006 Dec;98(6):1149-53.
15. Cantwell AL, Bogache WK, Richardson SF, Tutrone RF, Barkin J, Fagelson JE, et al. Multicentre prospective crossover study of the 'prostatic urethral lift' for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *BJU Int.* 2014 Apr;113(4):615-22.
16. Cantrill CH, Zorn KC, Elterman DS, Gonzalez RR. The Rezūm system - a minimally invasive water vapor thermal therapy for obstructive benign prostatic hyperplasia. *Can J Urol.* 2019 Jun;26(3):9787-9793.
17. Carnevale FC, Iscaife A, Yoshinaga EM, Moreira AM, Antunes AA, Srougi M. Transurethral Resection of the Prostate (TURP) Versus Original and PERFecTED Prostate Artery Embolization (PAE) Due to Benign Prostatic Hyperplasia (BPH): Preliminary Results of a Single Center, Prospective, Urodynamic-Controlled Analysis. *Cardiovasc Intervent Radiol.* 2016 Jan;39(1):44-52.
18. Carnevale FC, Moreira AM, Harward SH, Bhatia S, de Assis AM, Srougi M, Cerri GG, Antunes AA. Recurrence of Lower Urinary Tract Symptoms Following Prostate Artery Embolization for Benign Hyperplasia: Single Center Experience Comparing Two Techniques. *Cardiovasc Intervent Radiol.* 2017 Mar;40(3):366-374.
19. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Jul 27, 2021. Available at URL address: [https://www.cms.gov/medicare-coverage-database/indexes/lcd-alphabetical-index.aspx?Cntrctr=373&ContrVer=1&CntrctrSelected=373\\*1&DocType=Active%7cFuture&s=All&bc=AggAAAQAAAA&](https://www.cms.gov/medicare-coverage-database/indexes/lcd-alphabetical-index.aspx?Cntrctr=373&ContrVer=1&CntrctrSelected=373*1&DocType=Active%7cFuture&s=All&bc=AggAAAQAAAA&)
20. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Jul 27, 2021. Available at URL address: <https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx>
21. Chin PT, Bolton DM, Jack G, Rashid P, Thavaseelan J, Yu RJ, et al. Prostatic urethral lift: two-year results after treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Urology.* 2012 Jan;79(1):5-11.
22. ClinicalTrials.org. Water Jet Ablation Therapy for Endoscopic Resection of Prostate Tissue (WATER). NCT02505919. First posted: July 21, 2015. Last update posted: April 8, 2020.
23. Corica F, Cheng L, Ramnani D, Dharamdas R, Pacelli A, Weaver A, et al. Transurethral hot-water balloon thermoablation for benign prostatic hyperplasia: patient tolerance and pathologic findings. *Urol.* 2000 Jul;56(1):76-81.
24. Daehlin L, Frugård J. Interstitial laser coagulation in the management of lower urinary tract symptoms suggestive of bladder outlet obstruction from benign prostatic hyperplasia: long-term follow-up. *BJU Int.* 2007 Jul;100(1):89-93.
25. Darson MF, Alexander EE, Schiffman ZJ, Lewitton M, Light RA, Sutton MA, Delgado-Rodriguez C, Gonzalez RR. Procedural techniques and multicenter postmarket experience using minimally invasive convective radiofrequency thermal therapy with Rezūm system for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. *Res Rep Urol.* 2017 Aug 21;9:159-168.
26. de Assis AM, Moreira AM, de Paula Rodrigues VC, Yoshinaga EM, Antunes AA, Harward SH, et al. Prostatic artery embolization for treatment of benign prostatic hyperplasia in patients with prostates > 90 g: a prospective single-center study. *J Vasc Interv Radiol.* 2015 Jan;26(1):87-93.

27. Dineen MK, Shore ND, Lumerman JH, Saslawsky MJ, Corica AP. Use of a temporary prostatic stent after transurethral microwave thermotherapy reduced voiding symptoms and bother without exacerbating irritative symptoms. *Urology*. 2008;71(5):873-77.
28. Dixon C, Cedano ER, Pacik D, Vit V, Varga G, Wagrell L, Tornblom M, Mynderse L, Larson T. Efficacy and Safety of Rezūm System Water Vapor Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *Urology*. 2015b Nov;86(5):1042-7.
29. Dixon CM, Cedano ER, Pacik D, Vit V, Varga G, Wagrell L, et al. Two-year results after convective radiofrequency water vapor thermal therapy of symptomatic benign prostatic hyperplasia. *Res Rep Urol*. 2016 Nov 21;8:207-216.
30. Dixon CM, Rijo Cedano E, Mynderse LA, Larson TR. Transurethral convective water vapor as a treatment for lower urinary tract symptomatology due to benign prostatic hyperplasia using the Rezūm® system: evaluation of acute ablative capabilities in the human prostate. *Res Rep Urol*. 2015a Jan 30;7:13-8.
31. Elterman D, Gilling P, Roehrborn C, et al. Meta-analysis with individual data of functional outcomes following Aquablation for lower urinary tract symptoms due to BPH in various prostate anatomies. *BMJ Surg Interv Health Technologies* 2021;3:e000090.
32. Fitzpatrick JM. Minimally invasive and endoscopic management of benign prostatic hyperplasia. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. *Campbell-Walsh Urology*, 10<sup>th</sup> ed. St. Louis: W.B. Saunders; 2011.
33. Gao YA, Huang Y, Zhang R, Yang YD, Zhang Q, Hou M, Wang Y. Benign prostatic hyperplasia: prostatic arterial embolization versus transurethral resection of the prostate--a prospective, randomized, and controlled clinical trial. *Radiology*. 2014 Mar;270(3):920-8.
34. Gilling P, Barber N, Bidair M, Anderson P, Sutton M, Aho T, et al. WATER: A Double-Blind, Randomized, Controlled Trial of Aquablation® vs Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia. *J Urol*. 2018 May;199(5):1252-1261.
35. Gilling PJ, Barber N, Bidair M, Anderson P, Sutton M, Aho T, et al. Randomized Controlled Trial of Aquablation versus Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia: One-year Outcomes. *Urology*. 2019 Mar;125:169-173.
36. Gilling P, Anderson P, Tan A. Aquablation of the Prostate for Symptomatic Benign Prostatic Hyperplasia: 1-Year Results. *J Urol*. 2017 Jun;197(6):1565-1572.
37. Gilling P, Reuther R, Kahokehr A, Fraundorfer M. Aquablation - image-guided robot-assisted waterjet ablation of the prostate: initial clinical experience. *BJU Int*. 2016 Jun;117(6):923-9.
38. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, et al. EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. *Eur Urol*. 2015 Jun;67(6):1099-109.
39. Gratzke C, Barber N, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prostatic urethral lift vs transurethral resection of the prostate: 2-year results of the BPH6 prospective, multicentre, randomized study. *BJU Int*. 2017 May;119(5):767-775.
40. Gravas S, Cornu JN, Gacci M, Gratzke C, Herrmann TRW, Mamoulakis C, Rieken M, Speakman MJ, Tikkinen KAO. Management of non-neurogenic male LUTS. Update 2021. Accessed Jul 27, 2021. Available at URL address: <https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/>

41. Green Z, Westwood J, Somani BK. What's New in Rezūm: a Transurethral Water Vapour Therapy for BPH. *Curr Urol Rep*. 2019 May 31;20(7):39.
42. Gupta N, Rogers T, Holland B, Helo S, Dynda D, McVary KT. Three-Year Treatment Outcomes of Water Vapor Thermal Therapy Compared to Doxazosin, Finasteride and Combination Drug Therapy in Men with Benign Prostatic Hyperplasia: Cohort Data from the MTOPS Trial. *J Urol*. 2018 Aug;200(2):405-413.
43. Hayes, Inc. Hayes Health Technology Assessment. Prostatic urethral lift (urolift system) for treatment of symptoms associated with benign prostatic hyperplasia. Hayes, Inc.; Jun 9, 2020.
44. Hayes, Inc. Hayes Prognosis Overview. Aquabeam aquablation waterjet tissue resection for BPH. Hayes, Inc.: January 2018; Archived April 29, 2019.
45. Hayes, Inc. Health Technology Assessment. Rezūm system (nxthera inc.) for benign prostatic hyperplasia. Hayes, Inc.: Feb 28, 2018. Annual Review Mar 12, 2020.
46. Hayes Inc. Hayes Comparative Effectiveness Review of Prostatic Artery Embolization (PAE) for Treatment of Benign Prostatic Hypertrophy (BPH). Hayes, Inc.: February 11, 2019. Amended August 21, 2019. Annual review May 15, 2020.
47. Hempel CR, Hall TL, Cain CA, Fowlkes JB, Xu Z, Roberts WW. Histotripsy fractionation of prostate tissue: local effects and systemic response in a canine model. *J Urol*. 2011 Apr;185(4):1484-9.
48. Hoffman RM, Monga M, Elliot SP, Macdonald R, Wilt TJ. Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database Sys Rev*. 2007 Oct 14;(4):CD004135.
49. Hwang EC, Jung JH, Borofsky M, Kim MH, Dahm P. Aquablation of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2019 Feb 13;2:CD013143.
50. Insausti I, Sáez de Ocáriz A, Galbete A, et al. Randomized comparison of prostatic artery embolization versus transurethral resection of the prostate for treatment of benign prostatic hyperplasia. *Journal of vascular and interventional radiology : JVIR*. 2020.
51. Jiang YL, Qian LJ. Transurethral resection of the prostate versus prostatic artery embolization in the treatment of benign prostatic hyperplasia: a meta-analysis. *BMC Urol*. 2019 Jan 28;19(1):11.
52. Jones P, Rai BP, Nair R, Somani BK. Current Status of Prostate Artery Embolization for Lower Urinary Tract Symptoms: Review of World Literature. *Urology*. 2015 Oct;86(4):676-81.
53. Jones P, Rajkumar GN, Rai BP, Aboumarzouk OM, Cleaveland P, Srirangam SJ, Somani BK. Medium-term Outcomes of Urolift (Minimum 12 Months Follow-up): Evidence From a Systematic Review. *Urology*. 2016 Nov;97:20-24.
54. Jung JH, Reddy B, McCutcheon KA, Borofsky M, Narayan V, Kim MH, Dahm P. Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews* 2019, Issue 5. Art. No.: CD012832.
55. Kasivisvanathan V, Hussain M. Aquablation versus transurethral resection of the prostate: 1 year United States - cohort outcomes. *Can J Urol*. 2018 Jun;25(3):9317-9322.
56. Koca O, Keleş MO, Kaya C, Güneş M, Öztürk M, Karaman Mİ. Plasmakinetic vaporization versus transurethral resection of the prostate: Six-year results. *Turk J Urol*. 2014 Sep;40(3):134-7.
57. Kuang M, Vu A, Athreya S. A Systematic Review of Prostatic Artery Embolization in the Treatment of Symptomatic Benign Prostatic Hyperplasia. *Cardiovasc Intervent Radiol*. 2017 May;40(5):655-663.



58. Li Y, Zhao Q, Dong L. Efficacy and safety of ultrasound-guided transrectal ethanol injection for the treatment of benign prostatic hyperplasia in patients with high-risk comorbidities: a long-term study at a single tertiary care institution. *Urology*. 2014 Mar;83(3):586-91
59. Lourenco T, Pickard R, Vale L, Grant A, Fraser C, MacLennan G, N'Dow J. Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomised controlled trials. *BMJ*. 2008b Jun 30;337:a449.
60. Lusuardi L, Hruby S, Janetschek G. New emerging technologies in benign prostatic hyperplasia. *Curr Opin Urol*. 2013 Jan;23(1):25-9.
61. Magistro G, Chapple CR, Elhilali M, Gilling P, McVary KT, Roehrborn CG, Stief CG, Woo HH, Gratzke C. Emerging Minimally Invasive Treatment Options for Male Lower Urinary Tract Symptoms. *Eur Urol*. 2017 Dec;72(6):986-997.
62. Magno C, Mucciardi G, Gali A, Anastasi G, Infrerra A, Morgia G. Transurethral ethanol ablation of the prostate (TEAP): an effective minimally invasive treatment alternative to traditional surgery for symptomatic benign prostatic hyperplasia (BPH) in high-risk comorbidity patients. *Int Urol Nephrol*. 2008;40(4):941-6.
63. Malling B, Røder MA, Brasso K, Forman J, Taudorf M, Lönn L. Prostate artery embolisation for benign prostatic hyperplasia: a systematic review and meta-analysis. *Eur Radiol*. 2019;29(1):287-298.
64. Marcon J, Magistro G, Stief CG, Grimm T. What's New in TIND? *Eur Urol Focus*. 2018 Jan;4(1):40-42.
65. Mattiasson A, Wagrell L, Schelin S, Nordling J, Richthoff J, Maggnuson B, et al. Five-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. *Urology*. 2007 Jan;29(1):91-6.
66. McNicholas TA, Woo HH, Chin PT, Bolton D, Fernández Arjona M, Sievert KD, et al. Minimally invasive prostatic urethral lift: surgical technique and multinational experience. *Eur Urol*. 2013 Aug;64(2):292-9.
67. McNicholas TA. Benign prostatic hyperplasia and new treatment options – a critical appraisal of the UroLift system. *Med Devices (Auckl)*. 2016 May 19;9:115-23.
68. McVary KT, Roehrborn CG. Three-Year Outcomes of the Prospective, Randomized Controlled Rezūm System Study: Convective Radiofrequency Thermal Therapy for Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *Urology*. 2018 Jan;111:1-9.
69. McVary KT, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, et al. Minimally Invasive Prostate Convective Water Vapor Energy Ablation: A Multicenter, Randomized, Controlled Study for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *J Urol*. 2016a May;195(5):1529-38.
70. McVary KT, Gange SN, Shore ND, Bolton DM, Cowan BE, Brown BT, et al; L.I.F.T. Study Investigators. Treatment of LUTS secondary to BPH while preserving sexual function: randomized controlled study of prostatic urethral lift. *J Sex Med*. 2014 Jan;11(1):279-87.
71. McVary KT, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, et al. Erectile and Ejaculatory Function Preserved With Convective Water Vapor Energy Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: Randomized Controlled Study. *J Sex Med*. 2016b Jun;13(6):924-33.

72. McVary KT, Rogers T, Roehrborn CG. Rezūm Water Vapor Thermal Therapy for Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia: 4-Year Results From Randomized Controlled Study. *Urology*. 2019 Apr;126:171-179.
73. McVary KT, Rogers T, Mahon J, Gupta NK. Is Sexual Function Better Preserved After Water Vapor Thermal Therapy or Medical Therapy for Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia? *J Sex Med*. 2018 Dec;15(12):1728-1738.
74. McWilliams JP, Kuo MD, Rose SC, Bagla S, Caplin DM, Cohen EI, et al; Society of Interventional Radiology. Society of Interventional Radiology position statement: prostate artery embolization for treatment of benign disease of the prostate. *J Vasc Interv Radiol*. 2014 Sep;25(9):1349-51.
75. Minardi D, Galosi AB, Yehia M, Cristalli A, Hanitzsch H, Polito M, Muzzonigro G. Transurethral resection versus minimally invasive treatments of benign prostatic hyperplasia: results of treatments. Our experience. *Arch Ital Urol Androl*. 2004 Mar;76(1):11-8.
76. Moul JW, Whitley BM. Men's Health. Benign prostatic hyperplasia. In: Bope ET, Kellerman R, Rakel RE, editors. *Conn's Current Therapy 2019*, Philadelphia, PA: Saunders Elsevier; 1088-91.
77. Mynderse LA, Hanson D, Robb RA, Pacik D, Vit V, Varga G, et al. Rezūm System Water Vapor Treatment for Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia: Validation of Convective Thermal Energy Transfer and Characterization With Magnetic Resonance Imaging and 3-Dimensional Renderings. *Urology*. 2015 Jul;86(1):122-7.
78. Nair SM, Pimentel MA, Gilling PJ. Evolving and investigational therapies for benign prostatic hyperplasia. *Can J Urol*. 2015 Oct;22 Suppl 1:82-7.
79. Napal Lecumberri S, Insausti Gorbea I, Sáez de Ocáriz García A, Solchaga Álvarez S, Cebrián Lostal JL, Monreal Beortegui R, et al. Prostatic artery embolization versus transurethral resection of the prostate in the treatment of benign prostatic hyperplasia: protocol for a non-inferiority clinical trial. *Res Rep Urol*. 2018 Feb 13;10:17-22.
80. National Institute for Clinical Excellence (NICE). Prostatic urethral temporary implant insertion for lower urinary tract symptoms caused by benign prostatic hyperplasia. IPG641. Jan 2019. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/ipg641>
81. National Institute for Clinical Excellence (NICE). Transurethral water jet ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia. IPG629. Sep 2018. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/ipg629>
82. National Institute for Clinical Excellence (NICE). UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia. MTG58. May 2021. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/MTG58>
83. National Institute for Clinical Excellence (NICE). Prostate artery embolisation for lower urinary tract symptoms caused by benign prostate hyperplasia. IPG611. April 2018. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/ipg611>
84. National Institute for Clinical Excellence (NICE). Lower urinary tract symptoms in men: management. Clinical Guideline 97. May 2010. Last updated June 2015. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/cg97>
85. National Institute for Clinical Excellence (NICE). Rezum for treating lower urinary tract symptoms secondary to benign prostatic hyperplasia. MTG49. Jun 2020. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/mtg49>

86. National Institute for Clinical Excellence (NICE). Transurethral water vapour ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia. IPG625. Aug 2018. Accessed Jul 27, 2021. Available at URL address: <https://www.nice.org.uk/guidance/ipg625>
87. National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC, NIH). Prostate enlargement: benign prostatic hyperplasia. September 2014. Accessed Jul 27, 2021. Available at URL address: <https://www.niddk.nih.gov/health-information/urologic-diseases/prostate-problems/prostate-enlargement-benign-prostatic-hyperplasia#treatment>
88. NeoTract, Inc. UroLift™ System. Accessed Aug 10, 2020. Available at URL address: <http://www.neotract.com/>
89. Ng CS, Ulchaker JC, Kursh ED. Prospective evaluation of interstitial laser coagulation of the prostate: importance of surgical technique and patient selection. *J Endourol.* 2005 Oct;19(8):1012-5.
90. Nickel JC, Aaron L, Barkin J, Elterman D, Nachabé M, Zorn KC. Canadian Urological Association guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH): 2018 update. *Can Urol Assoc J.* 2018 Oct;12(10):303-312.
91. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al; European Association of Urology. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol.* 2013 Jul;64(1):118-40.
92. Medical Advisory Secretariat. Energy delivery systems for treatment of benign prostatic hyperplasia: an evidence-based analysis. *Ont Health Technol Assess Ser.* 2006;6(17):1-121.
93. Ostrem.T. Safety and efficacy of transurethral needle ablation of the prostate for symptomatic outlet obstruction. *Br J Urol.* 1998 May; 81(5):780-6.
94. Perera M, Roberts MJ, Doi SA, Bolton D. Prostatic urethral lift improves urinary symptoms and flow while preserving sexual function for men with benign prostatic hyperplasia: a systematic review and meta-analysis. *Eur Urol.* 2015 Apr;67(4):704-13.
95. Pimentel MA, Yassaie O, Gilling P. Urodynamic Outcomes After Aquablation. *Urology.* 2019 Apr;126:165-170.
96. Pisco JM, Bilhim T, Costa NV, et al. Randomised clinical trial of prostatic artery embolisation versus a sham procedure for benign prostatic hyperplasia. *European urology.* 2020;77(3):354-362.
97. Pisco JM, Rio Tinto H, Campos Pinheiro L, Bilhim T, Duarte M, Fernandes L, et al. Embolisation of prostatic arteries as treatment of moderate to severe lower urinary symptoms (LUTS) secondary to benign hyperplasia: results of short- and mid-term follow-up. *Eur Radiol.* 2013 Sep;23(9):2561-72.
98. Plante M, Gilling P, Barber N, Bidair M, Anderson P, Sutton M, et al. Symptom relief and anejaculation after aquablation or transurethral resection of the prostate: subgroup analysis from a blinded randomized trial. *BJU Int.* 2019 Apr;123(4):651-660.
99. Porpiglia F, Fiori C, Amparore D, et al. Second-generation of temporary implantable nitinol device for the relief of lower urinary tract symptoms due to benign prostatic hyperplasia: results of a prospective, multicentre study at 1 year of follow-up. *BJU Int.* 2019;123(6):1061-1069.
100. Porpiglia F, Fiori C, Bertolo R, Garrou D, Cattaneo G, Amparore D. Temporary implantable nitinol device (TIND): a novel, minimally invasive treatment for relief of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH): feasibility, safety and functional results at 1 year of follow-up. *BJU Int.* 2015 Aug;116(2):278-87.

101. Porpiglia F, Fiori C, Bertolo R, Giordano A, Checcucci E, Garrou D, et al. 3-Year follow-up of temporary implantable nitinol device implantation for the treatment of benign prostatic obstruction. *BJU Int.* 2018 Jul;122(1):106-112.
102. Pyo JS, Cho WJ. Systematic review and meta-analysis of prostatic artery embolisation for lower urinary tract symptoms related to benign prostatic hyperplasia. *Clin Radiol.* 2017 Jan;72(1):16-22.
103. Qiu Z, Zhang C, Wang X, Cheng K, Liang X, Wang D, et al. Clinical evaluation of embolization of the superior vesical prostatic artery for treatment of benign prostatic hyperplasia: a single-center retrospective study. *Wideochir Inne Tech Maloinwazyjne.* 2017 Dec;12(4):409-416.
104. Ray A, Morgan H, Wilkes A, Carter K, Carolan-Rees G. The Urolift System for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A NICE Medical Technology Guidance. *Appl Health Econ Health Policy.* 2016 Oct;14(5):515-26.
105. Ray AF, Powell J, Speakman MJ, Longford NT, DasGupta R, Bryant T, et al. Efficacy and safety of prostate artery embolization for benign prostatic hyperplasia: an observational study and propensity-matched comparison with transurethral resection of the prostate (theUK-ROPE study). *BJU Int.* 2018 Aug;122(2):270-282.
106. Roehrborn C, Preminger G, Newhall P, Densrent J, Razvi H, Chin J, et al. Microwave thermotherapy for benign prostatic hyperplasia with the Dornier Urowave: results of a randomized, double-blind, multicenter, sham-controlled trial. *Urol.* 1998 Jan;51(1):19-28.
107. Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, et al. Multi-Center Randomized Controlled Blinded Study of the Prostatic Urethral Lift for the Treatment of LUTS Associated with Prostate Enlargement Due to BPH: The L.I.F.T. Study. *J Urol.* 2013 Jun 10.
108. Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, et al. Durability of the prostatic urethral lift: two year results of the L.I.F.T. Study. *Urology Practice* 2015a (2); 1-7.
109. Roehrborn CG, Rukstalis DB, Barkin J, Gange SN, Shore ND, Giddens JL, et al. Three year results of the prostatic urethral L.I.F.T. study. *Can J Urol.* 2015b Jun;22(3):7772-82.
110. Roehrborn CG, Barkin J, Gange SN, Shore ND, Giddens JL, Bolton DM, et al. Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. *Can J Urol.* 2017a Jun;24(3):8802-8813.
111. Roehrborn CG. Prostatic Urethral Lift: A Unique Minimally Invasive Surgical Treatment of Male Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *Urol Clin North Am.* 2016 Aug;43(3):357-69.
112. Roehrborn CG, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, et al. Convective Thermal Therapy: Durable 2-Year Results of Randomized Controlled and Prospective Crossover Studies for Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *J Urol.* 2017b Jun;197(6):1507-1516.
113. Russo GI, Kurbatov D, Sansalone S, Lepetukhin A, Dubsky S, Sitkin I, et al. Prostatic Arterial Embolization vs Open Prostatectomy: A 1-Year Matched-pair Analysis of Functional Outcomes and Morbidities. *Urology.* 2015 Aug;86(2):343-8.
114. Rukstalis D, Rashid P, Bogache WK, Tutrone RF, Barkin J, Chin PT, et al. 24-month durability after crossover to the prostatic urethral lift from randomised, blinded sham. *BJU Int.* 2016 Oct;118 Suppl 3:14-22.

115. Rukstalis D, Grier D, Stroup SP, Tutrone R, deSouza E, Freedman S, David R, Kamientsky J, Eure G. Prostatic Urethral Lift (PUL) for obstructive median lobes: 12 month results of the MedLift Study. *Prostate Cancer Prostatic Dis.* 2019 Sep;22(3):411-419.
116. Ruszat R, Wyler SF, Seitz M, Lehmann K, Abe C, Bonkat G, et al. Comparison of potassium-titanyl-phosphate laser vaporization of the prostate and transurethral resection of the prostate: update of a prospective non-randomized two-centre study. *BJU Int.* 2008 Jul 29.
117. Sakr M, Eid A, Shoukry M, Fayed A. Transurethral ethanol injection therapy of benign prostatic hyperplasia: four-year follow-up. *Int J Urol.* 2009 Feb;16(2):196-201.
118. Sánchez-Gómez LM, Polo-deSantos M, Gómez-Sancha F, Luengo-Matos S. Efficacy and safety of the urolift® system for the treatment of benign prostate hyperplasia symptoms: systematic review. *Actas Urol Esp.* 2015 Jun;39(5):311-9.
119. Schuster TG, Wei JT, Hendlin K, Jahnke R, Roberts WW. Histotripsy Treatment of Benign Prostatic Enlargement Using the Vortex R(x) System: Initial Human Safety and Efficacy Outcomes. *Urology.* 2018 Apr;114:184-187.
120. Seki N, Nomura H, Yamaguchi A, Naito S. Effects of photoselective vaporization of the prostate on urodynamics in patients with benign prostatic hyperplasia. *J Urol.* 2008 Sep;180(3):1024-8.
121. Shah BB, Tayon K, Madiraju S, Carrion RE, Perito P. Prostatic Urethral Lift: Does Size Matter? *J Endourol.* 2018 Jul;32(7):635-638.
122. Shore N, Freedman S, Gange S, Moseley W, Heron S, Tutrone R, Brown T, Barkin J. Prospective multi-center study elucidating patient experience after prostatic urethral lift. *Can J Urol.* 2014 Feb;21(1):7094-101.
123. Shore N. A Review of the Prostatic Urethral Lift for Lower Urinary Tract Symptoms: Symptom Relief, Flow Improvement, and Preservation of Sexual Function in Men With Benign Prostatic Hyperplasia. *Curr Bladder Dysfunct Rep.* 2015;10(2):186-192.
124. Sievert KD, Schonhaler M, Berges R, Toomey P, Drager D, Herlemann A, et al. Minimally invasive prostatic urethral lift (PUL) efficacious in TURP candidates: a multicenter German evaluation after 2 years. *World J Urol.* 2019 Jul;37(7):1353-1360.
125. Sønksen J, Barber NJ, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prospective, Randomized, Multinational Study of Prostatic Urethral Lift Versus Transurethral Resection of the Prostate: 12-month Results from the BPH6 Study. *Eur Urol.* 2015 Apr 30.
126. Sountoulides P, Karatzas A, Gravas S. Current and emerging mechanical minimally invasive therapies for benign prostatic obstruction. *Ther Adv Urol.* 2019 Feb 14;11:1756287219828971.
127. Tanneru K, Gautam S, Norez D, Kumar J, Alam MU, Koocheckpour S, Balaji KC, Joseph C. Meta-analysis and systematic review of intermediate-term follow-up of prostatic urethral lift for benign prostatic hyperplasia. *Int Urol Nephrol.* 2020 Jun;52(6):999-1008.
128. Toohar R, Sutherland P, Costello A, Gilling P, Rees G, Maddern G. A systematic review of holmium laser prostatectomy for benign prostatic hyperplasia. *J Urol.* 2004 May;171(5):1773-81.
129. Tugcu V, Tasci AI, Sahin S, Zorluoglu F. Comparison of Photoselective Vaporization of the Prostate and Transurethral Resection of the Prostate: A Prospective Nonrandomized Bicenter Trial with 2-Year Follow-Up. *J Endourol.* 2008 Jul 9.

130. U.S. Food and Drug Administration. Center for devices and radiological health (CDRH). Rockville (MD): U.S. Department of Health and Human Services. iTind. DEN190020. Feb 25, 2020. Accessed Jul 27, 2021. Available at URL address: [https://www.accessdata.fda.gov/cdrh\\_docs/pdf19/DEN190020.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf19/DEN190020.pdf)
131. U.S. Food and Drug Administration. Center for devices and radiological health (CDRH). Rockville (MD): U.S. Department of Health and Human Services. De Novo Classification request for Aquabeam System: DEN170024. December 21, 2017. Accessed Jul 27, 2021. Available at URL address: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm?ID=DEN170024>
132. U.S. Food and Drug Administration. Center for devices and radiological health (CDRH). Rockville (MD): U.S. Department of Health and Human Services. 510k Premarket notification: Rezūm System. K150786. September 12, 2016. Accessed Jul 27, 2021. Available at URL address: [https://www.accessdata.fda.gov/cdrh\\_docs/pdf15/K150786.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150786.pdf)
133. U.S. Food and Drug Administration. Center for devices and radiological health (CDRH). Rockville (MD): U.S. Department of Health and Human Services. 510k Premarket notification: UroLift system. K130651. Accessed Jul 27, 2021. Available at URL address: [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/K130651.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K130651.pdf)
134. U.S. Food and Drug Administration. Center for devices and radiological health (CDRH). Rockville (MD): U.S. Department of Health and Human Services. 510k Premarket notification: Thermoflex system. Accessed Jul 27, 2021. Available at URL address: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?db=PMN&id=k000508>
135. U.S. Food and Drug Administration. Center for devices and radiological health (CDRH). Rockville (MD): U.S. Department of Health and Human Services. 510k Premarket notification: Visual-ICE Cryoablation System. Page Last Updated: Jul 26, 2021. Accessed Jul 28, 2021. Available at URL address: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K113860>
136. VanderBrink BA, Rastinehad AR, Badlani GH. Prostatic stents for the treatment of benign prostatic hyperplasia. *Curr Opin Urol.* 2007 Jan;17(1):1-6.
137. van Melick H, van Venrooj G, Eckhardt G, Boon T. A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: analysis of subjective changes, morbidity and mortality. *J Urol.* 2003 Apr;169(4):1411-16.
138. Walsh LP. State of the art: Advanced techniques for prostatic urethral lift for the relief of prostate obstruction under local anesthesia. *Can J Urol.* 2017 Jun;24(3):8859-8864.
139. Wang M, Guo L, Duan F, Yuan K, Zhang G, Li K, et al. Prostatic arterial embolization for the treatment of lower urinary tract symptoms as a result of large benign prostatic hyperplasia: A prospective single-center investigation. *Int J Urol.* 2015 Aug;22(8):766-72.
140. Wang XY, Zong HT, Zhang Y. Efficacy and safety of prostate artery embolization on lower urinary tract symptoms related to benign prostatic hyperplasia: a systematic review and meta-analysis. *Clin Interv Aging.* 2016 Nov 11;11:1609-1622.
141. Westenberg A, Gilling P, Kennet K, Frampton C, Fraundorfer M. Holmium laser resection of the prostate versus transurethral resection of the prostate: results of a randomized trial with 4-year minimum long-term follow-up. *J Urol.* 2004 Aug;172(2):616-19.
142. Wilson LC, Gilling PJ, Williams A, Kennett KM, Frampton CM, Westenberg AM. A randomised trial comparing holmium laser enucleation versus transurethral resection in the treatment of prostates larger than 40 grams: results at 2 years. *Eur Urol.* 2006 May 2.

143. Woo HH, Bolton DM, Laborde E, Jack G, Chin PT, Rashid P, et al. Preservation of sexual function with the prostatic urethral lift: a novel treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Sex Med.* 2012 Feb;9(2):568-75.
144. Woo HH, Chin PT, McNicholas TA, Gill HS, Plante MK, Bruskewitz RC, Roehrborn CG. Safety and feasibility of the prostatic urethral lift: a novel, minimally invasive treatment for lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). *BJU Int.* 2011 Jul;108(1):82-8.
145. Woo HH, Gonzalez RR. Perspective on the Rezūm® System: a minimally invasive treatment strategy for benign prostatic hyperplasia using convective radiofrequency water vapor thermal therapy. *Med Devices (Auckl).* 2017 Apr 27;10:71-80.
146. Yang Q, Peters T, Donovan J, Wilt T, Abrams P. Transurethral incision compared with transurethral resection of prostate for bladder outlet obstruction: systematic review and meta-analysis of randomized controlled trials. *J Urol.* 2001;165(5):1526-32.
147. Zhang B, Wu G, Chen C, Song B, Li X, Zhong L, Wang H. Combination of channel-TURP and ILC versus standard TURP or ILC for elderly with benign prostatic hyperplasia: a randomized prospective trial. *Urol Int.* 2011;87(4):392-9.
148. Zumstein V, Betschart P, Vetterlein MW, Kluth LA, Hechelhammer L, Mordasini L, et al. Prostatic Artery Embolization versus Standard Surgical Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis. *Eur Urol Focus.* 2018 Oct 3.

---

"Cigna Companies" refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2021 Cigna.