Benign Prostatic Hyperplasia

Number: 0079

POLICY

**Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers the following approaches to the treatment of benign prostatic hypertrophy (BPH) medically necessary for members with benign prostatic hypertrophy as alternatives to transurethral resection of the prostate (TURP):

A. Alpha adrenergic blockers (alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin)
B. Aquablation (AquaBeam, water jet hydrodissection)
C. Hormonal manipulation (including finasteride, dutasteride, and dutasteride plus tamsulosin)
D. Interstitial laser coagulation of the prostate (ILCP)
E. Laser prostatectomy
F. Laser based procedures including contact laser ablation of the prostate (CLAP), holmium laser procedures of the prostate (HoLAP, HoLEP, HoLRP), photoselective laser vaporization of the prostate (PVP), transurethral ultrasound-guided laser induced prostatectomy (TULIP), and visually-guided laser ablation of the prostate (VLAP, also called non-contact laser ablation of the prostate)
G. Prostatic urethral lift (e.g., the UroLift; usually 4 to 6 UroLift Implants are placed into the prostate)

POLICY HISTORY
Last Review: 04/26/2022
Effective: 11/17/1995
Next Review: 01/12/2023

H. Tadalafil (5 mg daily dose) (Note: Some plans exclude coverage of tadalafil; please check benefit plan descriptions)
I. Transurethral electrovaporization of the prostate (TUVP)
J. Transurethral incision of the prostate (TUIP)
K. Transurethral microwave thermotherapy (TUMT)
L. Transurethral needle ablation (TUNA), also known as transurethral radiofrequency needle ablation (RFNA) (including TUNA using water vapor, Rezum system (also known as convective radiofrequency transurethral water vapor therapy))
M. Ultrasonic aspiration.

Laser prostatecctomy, ILCP, other laser based prostate procedures, prostatic urethral lift, TUVP, TUIP, TUMT, TUNA and ultrasonic aspiration of prostate are experimental and investigational for other indications. See also CPB 0100 - Cryoablation (../100_199/0100.html).

II. Aetna considers the UroLume endourethral prosthesis (urethral stent) medically necessary to relieve prostatic obstruction secondary to BPH in men at least 60 years of age, or men under 60 years of age who are poor surgical candidates, and whose prostates are at least 2.5 cm in length. (Note: UroLume is not intended for temporary use).

UroLume endourethral prosthesis is also considered medically necessary for the treatment of recurrent bulbar urethral stenoses/strictures when previous therapeutic approaches such as dilation, urethrotomy or urethroplasty have failed (i.e., treatment was ineffective or there is recurrent stricture requiring additional treatment).

Aetna considers the UroLume endourethral prosthesis experimental and investigational for other indications because its effectiveness for indications other than the ones listed above has not been established.

III. Aetna considers the following approaches for the treatment of BPH experimental and investigational because the effectiveness of these interventions has not been established by the peer-reviewed

medical literature:

A. Absolute ethanol injection (transurethral)
B. Acupuncture
C. Bipolar plasma enucleation
D. Botulinum toxin
E. Cryosurgical ablation
F. Drug-coated balloons (e.g., the Optilume paclitaxel-coated balloon)
G. Endoscopic balloon dilation of the prostate
H. Histotripsy
I. Intra-prostatic injections of vitamin D3 receptor analogs
J. Lutenizing hormone-releasing hormone antagonists
K. Melatonin
L. Mirabegron (Myrbetriq)
M. MRI-guided laser focal ablation
N. Phytotherapy
O. Plasma kinetic vaporization (PlasmaKinetic Tissue Management System, Gyrus, Maple Grove, MN)
P. Prostatic arterial embolization (transcatheter embolization)
Q. Temporary prostatic urethral stent (including implantable nitinol devices)
R. Transrectal thermal therapy (including transrectal microwave hyperthermia, transrectal radiofrequency hyperthermia, transrectal electrothermal hyperthermia, and transrectal high-intensity focused ultrasound)
S. Water-induced thermotherapy (also known as hot-water balloon thermoablation and thermourethral hot-water therapy).
T. XFLO Expander System (Mercury Expander System)

IV. Aetna considers Prosta-Seq for diagnosis of benign prostatic hyperplasia (BPH) experimental and investigational because its effectiveness has not been established.

V. Aetna considers measurement of blood-based microRNAs, and seminal cell free DNA concentration for differential diagnosis of prostate cancer and BPH experimental and investigational because their effectiveness has not been established.

VI. Aetna considers CYP17 rs743572 polymorphism testing for estimating be BPH susceptibility experimental and investigational because the effectiveness of this approach has not been established.

Background

This policy is based primarily on the practice guideline of management of benign prostatic hyperplasia (BPH) from the American Urological Association. While a number of treatment modalities have been shown to be effective for BPH, it is not yet evident which of these techniques will prove to be superior or which will approach the effectiveness of transurethral resection of the prostate (TURP) in treating BPH.

Temporary stents are designed primarily for short-term use in the treatment of symptomatic BPH, for a duration of 6 months to 3 years (van Dijk and de la Rosette, 2003). Temporary stents are made of non-absorbable material, which prevents epithelial ingrowth and therefore allows easy removal. However, this may lead to unintended migration. Some temporary stents are biodegradable, so that they break down into small fragments, which are excreted through the urethra over time. Although no explantation of biodegradable stents is required, the excreted fragments may cause urethral obstruction.

According to the guidelines by the American Urological Association (AUA, 2003), "because prostatic stents are associated with significant complications, such as encrustation, infection and chronic pain, their placement should be considered only in high-risk patients, especially those with urinary retention". AUA guidelines explain: "Clinical trials of temporary prostatic stents are ongoing, and some long-term efficacy and safety studies have been published. It is unclear whether prostatic stents have applications in men with symptomatic BPH who have not developed urinary retention and whose medical conditions permit other forms of treatment."

One temporary prostatic urethral stent currently in development is the Spanner, which is designed for temporary use (30 days or less) in men with bladder outlet obstruction to reduce elevated post-void residual and improve voiding symptoms. The stent design is very similar to the proximal 4 to 6 cm portion of a Foley catheter. It includes a proximal balloon to prevent distal displacement, a urine port situated cephalad to the balloon, and a reinforced stent of various lengths to span most of the prostatic urethra. There is also a distal anchor mechanism attached by sutures, and a retrieval suture which extends to the meatus and deflates the proximal balloon when pulled.

Corica et al (2004) reported that the Spanner significantly improved voiding function and quality of life among patients with prostatic urethral obstruction (n = 30). However, in a review on recent developments in the management of symptomatic BPH, Ogiste and colleagues (2003) stated that the role of stents as an intermediary in cases of treatment failure, or as definitive therapy for BPH and its associated problems are still unclear, when compared with newer, minimally invasive options. Current literature on stents is relatively sparse. However, recent studies showed that permanent and temporary prostatic urethral stenting are effective in relieving obstruction and urinary retention. Nevertheless larger controlled clinical studies are needed to demonstrate the real value of this intervention.

Azuyma and Chancellor (2004) commented that although the results of the use of bioabsorbable spiral stents are encouraging, "there are still too many failures." The authors state that controlled studies are needed to compare bioabsorbable stents with other forms of therapy.

The California Technology Assessment Forum (2002) concluded that water-induced thermotherapy for BPH does not meet CTAF's technology assessment criteria. The assessment concluded that "[e]xisting studies have not yet demonstrated that WIT results in better health outcomes as much as or more than the established alternative of TURP, TUNA, or microwave thermotherapy." Furthermore, in a review on minimally invasive therapies for BPH, Naspro et al (2005) noted that "currently, transurethral microwave thermotherapy seems to offer the soundest basis for management of the condition, providing the longest term follow up and the largest numbers of studies completed to date. Among surgical

alternatives, holmium laser enucleation has gained ground as an encouraging new approach, being similar to standard transurethral resection of the prostate, but reducing perioperative morbidity with the same long-term results. More randomized comparisons correctly conducted need to be undertaken before an accurate general picture is available for the urologist".

Transurethral electrovaporization of the prostate (TUVP) is another alternative, minimally invasive procedures to treat BPH. This procedure combines electrosurgical vaporization and desiccation to remove obstructive hyperplastic prostatic tissue with minimal morbidity. It entails a special electrosurgical modification involving a grooved roller electrode with a large surface area and multiple edges of contact; thus allowing high current density to be delivered to an extensive area of tissue to be vaporized. The device fits standard resectoscopic equipment, and its use requires no special skills other than those needed for conventional TURP.

Fowler et al (2005) compared the clinical and cost-effectiveness of TUVP with TURP. Men requiring surgery for lower urinary tract symptoms deemed to be due to BPH were recruited from 4 centers in south-east England. Main outcome measures were the International Prostate Symptom Score (IPSS) and the IPSS quality of life (QOL) question. Secondary outcome measures included urinary flow rate, post-void urinary volume, prostate volume and pressure-flow urodynamics. TURP and TUVP were both effective in producing a clinically important reduction in IPSS and positive change in the IPSS QOL question. The success rate for relief of symptoms was 85 % for TURP and 74 % for TUVP. Neither the success of the treatment nor the change in aggregated IPSS was significantly different between the groups. The improvement was sustained to 24 months after treatment with no significant difference between the groups. The effectiveness of both treatments was also equivalent when assessed through improvement in objective measures of urinary tract function, reduction in prostate size and the change in health questions of SF-36. The absolute incidence of adverse events was similar between the 2 groups. The incidence of severe or prolonged bleeding was less with TUVP, as evidenced by the need for blood transfusion and the drop in hemoglobin level 24 hours post-operatively. This study did not show any significant difference in inpatient stay or use of outpatient resources between the groups. The authors concluded that

TURP and TUVP are equivalently effective in improving the symptoms of benign prostatic enlargement over at least 2 years. TUVP is associated with less morbidity due to hemorrhage than TURP. This finding is in agreement with that of the National Institute for Health and Clinical Excellence (2003), which stated that there is adequate support for the use of TUVP, and that of Nohuglu et al (2005) who found that TUVP is as effective as TURP with similar morbidity. The advantages of TUVP are that the urethral catheter is withdrawn earlier, hospitalization is shorter, and bleeding is less.

Thomas et al (2006) noted that botulinum neurotoxin (BoNT) application recently has been extended to prostate disorders. While BoNT has shown promising preliminary results for male lower urinary tract symptoms, and translational research suggests novel mechanism of action of BoNT in the prostate, it is important to remember that the application of BoNT in the prostate is not approved by the regulatory agencies and caution should be applied until larger randomized clinical trials are completed. This is in agreement with the observations of Azzouzi et al (2006) as well as Chuang and Chancellor (2006).

Kuo and Liu (2009) evaluated the effectiveness of BoNT-A in patients with large BPH with an unsatisfactory response to combined alpha-blocker and 5-alpha-reductase inhibitor therapy. A total of 60 patients with total prostate volume (TPV) of greater than 60 ml with unsatisfactory response to combination medical therapy were randomly assigned to receive add-on intra-prostatic BoNT-A injection (n = 30) or continued medical therapy (control group). Patients in the treatment group received 200 to 600 U of Botox injected into the prostate. Outcome parameters including IPSS, quality of life index (QOL-I), TPV, maximum flow rate (Q(max)) and post-void residual (PVR) volume were compared between treatment and control groups at baseline, 6 months and 12 months. Significant decreases in IPSS, QOL-I and TPV, and increase in Q(max) were observed at 6 months and remained stable at 12 months in the treatment group. Improvements in IPSS and QOL-I were also observed at 6 months and a decrease in TPV at 12 months was noted in the control group. However, no significant changes in any parameters except for QOL-I at 6 and 12 months were noted between the treatment and control groups. Acute urinary retention developed in 3 patients receiving BoNT-A treatment. Three BoNT-A and 2 medical treatment patients converted to

trans-urethral surgery at the end of study. The authors concluded that the findings of this study showed that add-on prostatic BoNT-A medical treatment can reduce prostate volume and improve lower urinary tract symptom score and QOL-I within 6 months in the treatment of large BPH. However, the therapeutic effect at 12 months was similar to combination medical treatment.

Oeconomou and Madersbacher (2010) summarized the mechanisms through which BoNT-A could inhibit the progression of BPH and eliminate the lower urinary tract symptoms (LUTS) according to the findings of animal studies. Furthermore, these researchers reviewed clinical studies to report the safety and effectiveness of intra-prostatic BoNT-A injection according to various injection protocols. The experimental studies reported induced relaxation of the prostate, atrophy, and reduction in its size through inhibition of the trophic effect of the autonomic system on the prostate gland. Also, a possible mechanism of reduction in LUTS might take place through inhibition of sensory afferents from the prostate to the spinal cord. Clinical studies reported symptomatic relief and improvement in the measured parameters during the follow-up period, whereas local or systematic side-effects are rare. The authors concluded that it should be recognized that, at present, this therapy is still experimental. Although the results of the clinical studies are encouraging, the level of evidence is low. Large-scale, clinical, placebo-controlled, randomized studies, including long-term surveillance to document the evidence of this therapy are needed.

In a phase II prospective study, Richter et al (2009) recorded the effectiveness and complications of holmium laser enucleation of the prostate (HoLEP) in the first post-operative year. Eighty-six of 343 consecutive patients with benign prostatic obstruction (IPSS greater than 10] were treated with the VersaPulse 100-W laser (Lumenis), 2.0 J/50 Hz or 3.2 J/25 Hz. Pre-operative and post-operative prostate-specific antigen (PSA), Q(max), IPSS, prostate gland volume, and PVR volume were prospectively measured. The median follow-up time was 8 months (3 to 21). Median patient age was 71 (50 to 83) years, and mean operating time was 77.5 (9 to 135) mins. There was only 1 case of significant bleeding. In 14 of 86 cases (16 %), HoLEP was combined with TURP. Short-term voiding complaints were expressed by 26.7 % of the questioned patients. The length of hospital stay was in most cases less

than 48 hrs. IPSS, Q(max), PSA, PVR volume, gland volumes, and QOL improved significantly after 3 months, and all parameters remained unchanged after 12 months. The re-operation rate within 12 months was 6.8 %. The authors concluded that the advantage of HoLEP over TURP is the very low bleeding rate and thus a shorter hospital stay and possible out-patient therapy. In particular, patients with prostate gland volume less than 50 mls profit from HoLEP. Post-operative voiding complaints are comparable to those with TURP. Moreover, the authors stated that long-term results are needed to confirm the low re-operation rate.

Erol et al (2009) prospectively evaluated vaporization efficiency of the high-power, 980-nm diode laser for bladder outlet obstruction due to BPH. A total of 47 consecutive patients were included in the study. Inclusion criteria were maximal flow rate 12 ml per second or less with voided volume 150 ml or greater, IPSS of 12 or greater, and QOL score 3 or greater. Patients with a history of neurogenic voiding dysfunction, chronic prostatitis, or prostate or bladder cancer were excluded from analysis. Pre-operative maximal flow rate, post-void residual urine, IPSS, QOL, International Index of Erectile Function-5, PSA, and prostate volume were compared with values at 3 and 6 months. Complications were assessed. Month 3 assessment revealed that the mean (+/- standard deviation [SD]) IPSS decreased significantly from 21.93 +/- 4.88 to 10.31 +/- 3.79 ($p = 0.0001$). The mean maximal flow rate increased significantly from 8.87 +/- 2.18 to 17.51 +/- 4.09 ml per second ($p = 0.0001$). Quality of life score changed considerably compared to baseline. All of these values showed slight improvement at month 6. There was no deterioration in erectile function according to the International Index of Erectile Function-5 short form. Post-void residual urine decreased significantly; reductions in prostate volume and PSA were also significant. The most common post-operative complications were retrograde ejaculation (13 of 41 patients or 31.7 %) and irritative symptoms (11 of 47 or 23.4 %), which subsided in the maximal flow rate at 2 weeks. Re-catheterization was necessary in 2 patients due to urinary retention after catheter removal; 2 patients had temporary combined urge and stress incontinence for 2 weeks. Late bleeding in 1 patient 4 weeks post-operatively resulted in catheterization and irrigation. The authors concluded that the high-power diode laser provided significant improvements in IPSS and the maximal flow rate with low morbidity. Thus, these results of prostate vaporization with the high-power diode

laser, representing what is to the authors' knowledge the first clinical study in the literature, are encouraging. The authors stated that further randomized clinical trials are needed to ascertain the role of high-power diode laser as an alternative to TURP or other laser techniques for BPH.

Van Cleynenbreugel et al (2009) presented recent clinical and urodynamic data on trans-urethral photo-selective vaporization of the prostate, and reported on the recent introduction of the 120-W GreenLight laser (GLL) high-performance system. These researchers noted that recent studies confirm improved urodynamic findings following GLL treatment. Moreover, it can be used safely in high-risk patients (e.g., those on anti-coagulant medication and patients with cardiopulmonary diseases), and has been proposed as an alternative to prostate enucleation for larger glands. The introduction of the 120-W high-performance system GLL does, however, place distinct demands on training and operative schemes. The authors concluded that the clinical results of GreenLight prostate vaporization are equivalent to those following TURP, with reduced operative risks, even for the high-risk patient. These clinical benefits have been confirmed by improved urodynamic parameters. Moreover, they noted that the potential advantages of the new 120-W high-performance system GLL have yet to be validated in larger randomized trials.

Ruszat et al (2008) evaluated the intermediate-term clinical effectiveness and the rate of complications in 80-W photo-selective vaporization of the prostate (PVP) with the potassium-titanyl-phosphate laser (GreenLight, Minnetonka, MN) compared with TURP in a prospective non-randomized 2-center study. A total of 396 patients (PVP = 269, TURP = 127) with lower urinary tract symptoms secondary to BPH were included in the study. There was a significant difference in mean age (72 years for PVP versus 68 for TURP, $p = 0.001$). Patients were therefore stratified in age categories (less than 70, 70 to 80, greater than 80 years) and compared for peri-operative variables, functional outcome and complications, with a follow-up of up to 24 months. The mean prostate size was greater (overall, 62 versus 48 mls, $p < 0.001$) and mean operative duration longer (overall 72 versus 53 mins; $p = 0.001$) for PVP in all age categories. The rate of intra-operative bleeding (3 % versus 11 %), blood transfusions (0 % versus 5.5 %) and capsule perforations (0.4 % versus 6.3 %), and early post-operative clot retention (0.4 % versus 3.9 %) was significantly

lower for PVP. Hospitalization time was significantly shorter in the PVP group for patients aged less than 70 years (3.0 versus 4.7 days) and 70 to 80 years (4.0 versus 5.0 days; p = 0.001). The improvement of peak urinary flow rate was higher after TURP for any age category. The IPSS and PVR volume during the follow-up showed no significant difference. After 12 months, the overall prostate size reduction was 63 % (-30 mls) after TURP and 44 % (-27 mls) after PVP. The rate of repeat TURP/PVP was higher in the PVP group (6.7 % versus 3.9 %, not significant) within the follow-up of up to 2 years. The incidence of urethral and bladder neck strictures was comparable. The authors concluded that PVP was more favorable in terms of peri-operative safety. Although patients assigned for PVP were older and had larger prostates, PVP resulted in a similar functional outcome. They stated that further follow-up is needed to draw final conclusions about the long-term effectiveness of PVP.

Naspro and colleagues (2009) noted that HoLEP and 532-nm laser vaporization of the prostate (with potassium titanyl phosphate [KTP] or lithium borate [LBO]) are promising alternatives to TURP and open prostatectomy (OP). These investigators evaluated the safety, effectiveness, and durability by analyzing the most recent evidence of both techniques, aiming to identify advantages, pitfalls, and unresolved issues. A Medline search of recently published data (2006 to 2008) regarding both techniques over the last 2 years (January 2006 to September 2008) was performed using evidence obtained from randomized trials (level of evidence: 1b), well-designed controlled studies without randomization (level of evidence: 2a), individual cohort studies (level of evidence: 2b), individual case control studies (level of evidence: 3), and case series (level of evidence: 4). In the last 2 years, several case-control and cohort studies have demonstrated reproducibility, safety, and effectiveness of HoLEP and 80-W KTP laser vaporization. Four randomized controlled trials (RCTs) were available for HoLEP, 2 compared with TURP and 2 compared with OP, with follow-up greater than 24 months. Results confirmed general effectiveness and durability of HoLEP, as compared with both standard techniques. Only 2 RCTs were available comparing KTP laser vaporization with TURP with short-term follow-up, and only 1 RCT was available comparing KTP laser vaporization with OP. The results confirmed the overall low peri-operative morbidity of KTP laser vaporization, although effectiveness was comparable to TURP in the short-term, despite a higher re-operation

rate. The authors concluded that although they are at different points of maturation, KTP or LBO laser vaporization and HoLEP are promising alternatives to both TURP and OP; KTP laser vaporization needs further evaluation to define the re-operation rate. Increasing the number of quality prospective RCTs with adequate follow-up is mandatory to tailor each technique to the right patient.

Chung and Te (2009) stated that traditionally, the gold standard for treatment of BPH has been the electrocautery-based TURP. However, the number of laser techniques being performed is rapidly increasing. Potential advantages of laser therapy over traditional TURP include decreased morbidity and shorter hospital stay. There are several techniques for laser prostatectomy that continue to evolve. The main competing techniques are currently the HoLEP and the 80-W 532-nm laser prostatectomy. The HoLEP, using the Holmium:YAG laser, has been shown to have clinical results similar to TURP and is suitable for patients on anti-coagulation as well as those with large prostates. Disadvantages of this technique are the high learning curve and requirement of a morcellator. When used to treat BPH, studies have demonstrated that, like the HoLEP, the 80-W KTP laser is safe and effective in patients with large prostates and in those taking oral anti-coagulation. Several studies have compared these 2 techniques to TURP. Frequently reported advantages of the HoLEP over the 80-W laser prostatectomy are the availability after the procedure of a pathology specimen and ability to remove a higher percentage of prostate tissue during resection. However, the trans-urethral laser enucleation of the prostate addresses these concerns and has shown to have durable outcomes at 2-year follow-up. Two new laser systems and techniques, the thulium laser and the 980-nm laser, have emerged recently. However, clinical data from these procedures are in their infancy and large long-term studies are needed to ascertain their clinical effectiveness.

Lourenco and colleagues (2008) ascertained the clinical effectiveness and cost utility of procedures alternative to TURP for BPH unresponsive to expectant, non-surgical treatments. Electronic searches of 13 databases to identify relevant RCTs were carried out. Two reviewers independently assessed study quality and extracted data. The International Prostate Symptom Score/American Urological Association (IPSS/AUA) symptom score was the primary outcome; others included

QOL, peak urine flow rate and adverse effects. Cost-effectiveness was assessed using a Markov model reflecting likely care pathways. A total of 156 reports describing 88 RCTs were included. Most had fewer than 100 participants (range of 12 to 234). It was found that TURP provided consistent, high-level, long-term symptomatic improvement. Minimally invasive procedures resulted in less marked improvement. Ablative procedures gave improvements equivalent to TURP. Furthermore, HoLEP resulted in greater improvement in flow rate. Holmium laser enucleation of the prostate is unique amongst the newer technologies in offering an advantage in urodynamic outcomes over TURP, although long-term follow-up data are lacking. Severe blood loss was more common following TURP. Rates of incontinence were similar across all interventions other than TUNA and laser coagulation, for which lower rates were reported. Acute retention and re-operation were commoner with newer technologies, especially minimally invasive interventions. The economic model suggested that minimally invasive procedures were unlikely to be cost-effective compared with TURP. Transurethral vaporization of the prostate was both less costly and less effective than TURP; whereas HoLEP was estimated to be more cost-effective than a single TURP but less effective than a strategy involving repeat TURP, if necessary. The base-case analysis suggested an 80 % chance that TUVP, followed by HoLEP if required, would be cost-effective at a threshold of 20,000 pounds per quality-adjusted life-year. At a 50,000 pounds threshold, TUVP, followed by TURP as required, would be cost-effective, although considerable uncertainty surrounds this finding. The main limitations are the quantity and quality of the data available, in the context of multiple comparisons. The authors concluded that in the absence of strong evidence in favor of newer methods, the standard – TURP – remains both clinically effective and cost-effective. There is a need for further research to establish: (i) how many years of medical treatment are necessary to offset the cost of treatment with a minimally invasive or ablative intervention, (ii) more cost-effective alternatives to TURP; and (iii) strategies to improve outcomes after TURP.

Hashim and Abrams (2010) noted that benign prostatic enlargement (BPE) leading to benign prostatic obstruction (BPO) affects an increasing number of men as they grow older. They can affect QOL and cause

LUTS including urinary retention. The currently available pharmacotherapies are alpha-blockers and 5-alpha reductase inhibitors, which may be effective but can have adverse effects and long-term compliance problems. Thus, it is important to find new medical treatments for LUTS/BPO and this review aimed to identify the potential future drugs undergoing clinical trials in this field. Articles were identified by means of a computerized Google, PubMed and Cochrane Library search over the last 10 years (using the following keywords: benign prostate hyperplasia, enlargement and obstruction) and a search of the PharmaProjects database. The exact etiology of BPH and its consequences, BPE and BPO, are not known; however, aging and functioning testes have been implicated. Several classes of drugs are currently undergoing clinical trials such as phosphodiesterase-5 (PDE5) inhibitors and lutenizing hormone-releasing hormone antagonists. Others include phytoestrogens, progestogens, NX1207 and PRX302. Some of these work by affecting testosterone level and, therefore, on the static component of BPO, while it is not known how the rest work. The authors stated that until the exact etiology of BPH/BPE/BPO is known, it is unlikely the cure for this disorder will be found.

Wang (2010) examined the use of PDE5 inhibitors for BPH/LUTS treatment and highlighted the clinical significance. Pre-clinical and clinical studies have provided promising evidence that PDE5 inhibitors may be an effective and well-tolerated treatment option for BPH/LUTS. Combination therapy using PDE5 inhibitors and alpha1-adrenergic blockers resulted in greater improvements in BPH/LUTS than did either drug alone. There has been increasing interest in the use of PDE5 inhibitors to treat BPH/LUTS. Combination of PDE5 inhibitors and alpha1-adrenergic blockers may have an additive beneficial effect on BPH/LUTS compared with monotherapy. Mechanisms of action of nitric oxide/cyclic guanosine monophosphate/PDE5 pathway in the treatment of BPH/LUTS deserve further investigations. The author concluded that larger-scale, well-designed clinical trials are needed to ascertain the safety, effectiveness and cost-effectiveness of PDE5 inhibitors in the treatment of LUTS secondary to BPH.

Andersson et al (2011) reviewed the published literature describing the pathophysiology of male LUTS, with an emphasis on mechanisms that may be modulated or improved by PDE5 inhibition. Literature (through

March 2010) was obtained via Medline searches and from the individual reviewers files. Articles were selected for review based on describing in-vitro, pre-clinical, or clinical studies of pathological processes contributing to LUTS, or possible effects of PDE5 inhibition in the lower urinary tract. Major mechanisms contributing to LUTS include: reduced nitric oxide/cyclic guanosine monophosphate signaling; increased RhoA kinase pathway activity; autonomic over-activity; increased bladder afferent activity; and pelvic ischemia. Tadalafil and other PDE5 inhibitors have demonstrated beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion that may impact LUTS in men. The authors concluded that the pathophysiology of male LUTS is complex and not completely understood. LUTS may occur independently of BPH or secondary to BPH but in both cases involve obstructive or irritative mechanisms with substantial pathophysiological overlap. While the precise mechanism remains unclear, inhibition of PDE5 seems to have an effect on several pathways that may impact LUTS.

On October 6, 2011, the FDA approved tadalafil (Cialis) for the treatment of BPH, and for the treatment of BPH and erectile dysfunction (ED), when the conditions occur simultaneously. Tadalafil should not be used in patients taking nitrates (e.g., nitroglycerin) because the combination can cause an unsafe decrease in blood pressure. Also, the use of tadalafil in combination with alpha blockers for the treatment of BPH is not recommended because the combination has not been adequately studied for the treatment of BPH, and there is a risk of lowering blood pressure. In 2 clinical trials, men with BPH who took 5 mg of tadalafil once-daily experienced a statistically significant improvement in their symptoms of BPH compared to men who were treated with placebo. The trials based their findings on a reduction in total IPSS scores. In a third study, men who experienced both erectile dysfunction (ED) and BPH and who took 5 mg of tadalafil once-daily had improvement in both their symptoms of BPH and in their ED compared to men who were treated with placebo. The improvement in ED was measured using the Erectile Function domain score of the International Index of Erectile Function.

While surgical resection and ablation using many different forms of energy remain the reference standard for BPH treatment, many patients seek a less invasive approach that will improve symptoms but not risk the complications associated with tissue removal. The UroLift system (NeoTract Inc., Pleasanton, CA) permanent implant is such a modality; it is delivered under cystoscopic visualization. The implant "holds open" the lateral prostatic lobes creating a passage through the obstructed prostatic urethra. Voiding and symptoms are significantly improved without the morbidity or possible complications following prostate resection. The entire procedure can be readily performed using local anesthesia (Barkin et al, 2012).

On September 13, 2013, the FDA approved the marketing of the UroLift, the first permanent implant to relieve low or blocked urine flow in men aged 50 and older with BPH. Minor adverse events reported included pain or burning during urination, blood in the urine, frequent or urgent need to urinate, incomplete emptying of the bladder, and decreased urine flow.

Chin et al (2012) evaluated the effectiveness of the prostatic urethral lift in relieving LUTS secondary to BPH. A total of 64 men, aged greater than or equal to 55 years, with moderate-to-severe symptomatic BPH were treated and followed-up at 6 Australian institutions. The treatment consisted of transurethral delivery of small implants to secure the prostatic lobes in an open condition, thereby reducing obstruction of the urethral lumen. The effectiveness, including International Prostate Symptom Score, quality of life, benign prostatic hyperplasia Impact Index, and peak urethral flow rate were assessed at 2 weeks and 3, 6, 12, and 24 months. The effect of this treatment of erectile and ejaculatory function was assessed using the Sexual Health Inventory for Men and Male Sexual Health Questionnaire for Ejaculatory Dysfunction. The prostatic urethral lift improved LUTS symptoms rapidly and durably. The International Prostate Symptom Score was reduced 42 % at 2 weeks, 49 % at 6 months, and 42 % at 2 years in evaluable patients. The peak flow rate improved by greater than or equal to 30 % (2.4 ml/s) at all intervals compared with baseline. No compromise in sexual function was observed after this treatment. The authors concluded that the findings of the present study demonstrated that LUTS and flow improvements

without compromising sexual function. Moreover, they stated that although this was an early study with a small cohort, this therapy showed promise as a new option for patients with LUTS.

Roehrborn et al (2013) reported the first multi-center randomized blinded trial of the prostatic urethral lift for the treatment of LUTS secondary to BPH. Men at least 50 years old with AUASI (American Urological Association Symptom Index) 13 or greater, a maximum flow rate 12 ml/s or less and a prostate 30 to 80 cc were randomized 2:1 between prostatic urethral lift and sham. In the prostatic urethral lift group, small permanent implants are placed within the prostate to retract encroaching lobes and open the prostatic urethra. Sham entailed rigid cystoscopy with sounds mimicking the prostatic urethral lift. The primary end-point was comparison of AUASI reduction at 3 months. The prostatic urethral lift arm subjects were followed to 1 year and assessed for LUTS, peak urinary flow rate, quality of life and sexual function. A total of 206 men were randomized (prostatic urethral lift 140 versus sham 66). The prostatic urethral lift and sham AUASI was reduced by 11.1 ± 7.67 and 5.9 ± 7.66, respectively ($p = 0.003$), thus meeting the primary end-point. Prostatic urethral lift subjects experienced AUASI reduction from 22.1 baseline to 18.0, 11.0 and 11.1 at 2 weeks, 3 months and 12 months, respectively, $p < 0.001$. Peak urinary flow rate increased 4.4 ml/s at 3 months and was sustained at 4.0 ml/s at 12 months, $p < 0.001$. Adverse events were typically mild and transient. There was no occurrence of de-novo ejaculatory or erectile dysfunction. The authors concluded that the prostatic urethral lift, inserted with the patient under local anesthesia, provided rapid and sustained improvement in symptoms and flow, while preserving sexual function.

McNicholas et al (2013) described the surgical technique and results of a novel minimally invasive implant procedure that offers symptom relief and improved voiding flow in an international series of patients. A total of 102 men with symptomatic BPH were consecutively treated at 7 centers across 5 countries. Patients were evaluated up to a median follow-up of 1 year post-procedure. Average age, prostate size, and IPSS were 68 years, 48 cm(3), and 23, respectively. The prostatic urethral lift mechanically opens the prostatic urethra with UroLift implants that were placed transurethrally under cystoscopic visualization, thereby separating the encroaching prostatic lobes. Patients were evaluated pre- and post-

operatively by the IPSS, QOL scale, Benign Prostatic Hyperplasia Impact Index, maximum flow rate (Qmax), and adverse event reports including sexual function. All procedures were completed successfully with a mean of 4.5 implants without serious adverse effects. Patients experienced symptom relief by 2 weeks that was sustained to 12 months. Mean IPSS, QOL, and Qmax improved 36 %, 39 %, and 38 % by 2 weeks, and 52 %, 53 %, and 51 % at 12 months ($p < 0.001$), respectively. Adverse events were mild and transient. There were no reports of loss of antegrade ejaculation. A total of 6.5% of patients progressed to TURP without complication. The authors concluded that prostatic urethral lift has promise for BPH. It is minimally invasive, can be done under local anesthesia, does not appear to cause retrograde ejaculation, and improves symptoms and voiding flow.

McVary et al (2014) analyzed data obtained from a randomized controlled blinded study of the prostatic urethral lift (PUL) to evaluate the sexual side effects of this novel treatment. Men greater than or equal to 50 years with prostates 30 to 80 cc, IPSS greater than 12, and Qmax less than or equal to 12 ml/s were randomized 2:1 between PUL and sham. Sexual activity was not an inclusion criterion. In PUL, permanent trans-prostatic implants were placed to retract encroaching lateral lobes and open the prostatic fossa. Sham entailed rigid cystoscopy with sounds to mimic PUL and a blinding screen. Blinded groups were compared at 3 months and active-arm then followed to 12 months for LUTS with IPSS and for sexual function with sexual health inventory for men (SHIM) and Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD). Subjects were censored from primary sexual function analysis if they had baseline SHIM less than 5 at enrollment. Secondary stratified analysis by ED severity was conducted. There was no evidence of degradation in erectile or ejaculatory function after PUL. SHIM and MSHQ-EjD scores were not different from control at 3 months but were modestly improved and statistically different from baseline at 1 year. Ejaculatory bother score was most improved with a 40 % improvement over baseline. Twelve-month SHIM was significantly improved from baseline for men entering the study with severe ED ($p = 0.016$). IPSS and Qmax were significantly superior to both control at 3 months and baseline at 1 year. There was no instance of de-novo sustained anejaculation or ED over the course of the study. The authors concluded that the PUL improved LUTS and urinary flow while preserving erectile and ejaculatory function.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2014) states: "Current evidence on the efficacy and safety of insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit."

Fernandes et al (2012) stated that prostatic artery embolization (PAE) gained special attention in the past years as a potential minimally invasive technique for BPH. Treatment decisions are based on morbidity and quality-of-life issues and the patient has a central role in decision-making. Medical therapy is a first-line treatment option and surgery is usually performed to improve symptoms and decrease the progression of disease in patients who develop complications or who have inadequately controlled symptoms on medical treatment. The use of validated questionnaires to assess disease severity and sexual function, uroflowmetry studies, prostate-specific antigen and prostate volume measurements are essential when evaluating patients before PAE and to evaluate response to treatment. The authors stated that PAE may be performed safely with minimal morbidity and without associated mortality. The minimally invasive nature of the technique inducing a significant improvement in symptom severity associated with prostate volume reduction and a slight improvement in the sexual function are major advantages. However, as with other surgical therapies for BPH, up to 15 % of patients fail to show improvement significantly after PAE, and there is a modest improvement of the peak urinary flow.

Pisco et al (2011) evaluated whether prostatic arterial embolization (PAE) might be a feasible procedure to treat lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). A total of 15 patients (age range of 62 to 82 years; mean age of 74.1 years) with symptomatic BPH after failure of medical treatment were selected for PAE with non-spherical 200-μm polyvinyl alcohol particles. The procedure was performed by a single femoral approach. Technical success was considered when selective prostatic arterial catheterization and embolization was achieved on at least one pelvic side. PAE was technically successful in 14 of the 15 patients (93.3 %). There was a mean follow-up of 7.9 months (range of 3 to 12 months). International Prostate Symptom Score decreased a mean of 6.5 points ($p = 0.005$),

quality of life improved 1.14 points (p = 0.065), International Index of Erectile Function increased 1.7 points (p = 0.063), and peak urinary flow increased 3.85 mL/sec (p = 0.015). There was a mean prostate-specific antigen reduction of 2.27 ng/ml (p = 0.072) and a mean prostate volume decrease of 26.5 mL (p = 0.0001) by ultrasound and 28.9 mL (p = 0.008) by magnetic resonance imaging. There was 1 major complication (a 1.5-cm(2) ischemic area of the bladder wall) and four clinical failures (28.6 %). The authors concluded that in this small group of patients, PAE was a feasible procedure, with preliminary results and short-term follow-up suggesting good symptom control without sexual dysfunction in suitable candidates, associated with a reduction in prostate volume.

Pisco et al (2013) evaluated the safety, morbidity, and short- and intermediate-term results of PAE for BPH after failure of medical treatment. Men older than 50 years with a diagnosis of BPH and moderate-to-severe lower urinary tract symptoms that were refractory to medical treatment for 6 months were eligible. PAE with non-spherical 80-180-μm (mean of 100-μm) and 180-300-μm (mean of 200-μm) polyvinyl alcohol particles was performed by means of a single femoral approach in most cases. Effectiveness variables of International Prostate Symptom Score (IPSS), quality of life (QOL) score, peak urinary flow, post-void residual volume, International Index Erectile Function (IIEF) score, prostate volume, and prostate-specific antigen level were assessed for up to 24 months after the procedure. Statistical analysis included the Kaplan-Meier method and random-effects generalized least squares regression with autoregressive disturbance. A total of 89 consecutive patients (mean age of 74.1 years) were included. PAE was technically successful in 86 of the 89 patients (97 %). Cumulative rates of clinical improvement in these patients were 78 % in the 54 patients evaluated at 6 months and 76 % in the 29 patients evaluated at 12 months. At 1-month follow-up, IPSS decreased by 10 points, QOL score decreased by 2 points, peak urinary flow increased by 38 %, prostate volume decreased by 20 %, post-void residual volume decreased by 30 ml, and IIEF score increased by 0.5 point (all differences were significant at p < 0.01). These changes were sustained throughout the observation period. There was one major complication: Intraluminal necrotic tissue attached to the bladder, which was removed with simple surgery and did not necessitate wall reconstruction. The authors concluded that PAE is a

safe and effective procedure, with low morbidity, no sexual dysfunction, and good short- and intermediate-term symptomatic control associated with prostate volume reduction.

The 3 aforementioned studies appear to have been carried out by the same group of investigators. These short- and intermediate-term findings need to be validated by well-designed studies.

Grosso et al (2015) reported the clinical outcome after PAE in 13 consecutive patients with BPH and LUTS. From May 2012 to October 2013, these investigators performed PAE in 13 consecutive patients (mean age of 75.9 years) with BPH and LUTS and refractory to medical therapy; 7 patients had an indwelling bladder catheter. Clinical follow-up (mean follow-up time of 244 days) was performed using the IPSS, QOL, the IIEF, blood PSA testing and transrectal prostatic ultrasound (US) scan with volume and weight calculation at 3, 6 and 12 months. Pre-procedural CT angiography (CTA) was done for vascular mapping. Embolization was performed using Embosphere (300 to 500 micron). Technical success was defined when selective PAE was completed in at least 1 pelvic side. Clinical success was defined when symptoms and QOL were improved. Prostatic artery embolization was technically successful in 12/13 patients (92 %). In 1 patient, PAE was not performed because of tortuosity and atherosclerosis of iliac arteries. Prostatic artery embolization was completed bilaterally in 9/13 (75 %) patients and unilaterally in 3 (27 %). All patients removed the bladder catheter from 4 days to 4 weeks after PAE. They obtained a reduction in IPSS (mean of 17.1 points), an increase in IIEF (mean of 2.6 points), an improvement in QOL (mean of 2.6 points) and a volume reduction (mean of 28 %) at 12 months. The authors concluded that consistent with the literature, their experience showed the feasibility, safety and efficacy of PAE in the management of patients with LUTS related to BPH. They stated that PAE may play an important role in patients in whom medical therapy has failed, and who are not candidates for surgery or TURP or refuse any surgical treatment. Moreover, they stated that larger case series and comparative studies with standard TURP can confirm the validity of the technique.

In a pilot study, Leoci et al (2014) studied the effectiveness of pulsed electromagnetic field therapy (PEMF) in dogs to modify prostate blood flow and evaluated its effect on BPH. Pulsed electromagnetic field therapy (5 mins, twice-daily for 3 weeks) was performed on 20 dogs affected by BPH. Prostatic volume, Doppler assessment by ultrasonography, libido, semen quality, testosterone levels, and seminal plasma volume, composition and pH were evaluated before and after treatment. The 3 weeks of PEMF produced a significant reduction in prostatic volume (average 57 %) without any interference with semen quality, testosterone levels or libido. Doppler parameters showed a reduction of peripheral resistances and a progressive reduction throughout the trial of the systolic peak velocity, end-diastolic velocity, mean velocity, mean, and peak gradient of the blood flow in the dorsal branch of the prostatic artery. The pulsatility index and the resistance index did not vary significantly over time. The authors concluded that the effectiveness of PEMF on BPH in dogs, with no side effects, suggested the suitability of this treatment in humans and supported the hypothesis that impairment of blood supply to the lower urinary tract may be a causative factor in the development of BPH.

Russo et al (2014) stated that BPH is a very common condition in men over 50 years, often resulting in LUTS. Medical therapy aims at improving QOL and preventing complications. The range of drugs available to treat LUTS is rapidly expanding. Silodosin is a relatively new alpha 1-adrenoreceptor antagonist that is selective for alpha 1A-adrenergic receptor. While causing smooth muscle relaxation in the lower urinary tract, it minimizes blood pressure-related adverse effects. Tadalafil, a PDEs type 5 inhibitor, is a drug recently approved for the treatment of BPH/LUTS that challenges the standard therapy with alpha 1-blockers, especially in men with concomitant ED. Mirabegron is the first beta 3-adrenoceptor agonist approved for the treatment of symptoms of overactive bladder. Benign prostatic hyperplasia-related detrusor overactivity (DO) may be successfully targeted by mirabegron. Gonadotropin-releasing hormone antagonists, intra-prostatic injections with NX-1207 and vitamin D3 receptor analogs exerted beneficial effects on LUTS but need further evaluation in clinical studies. The authors concluded that choosing the right treatment should be guided by patients' symptoms, co-morbidities and potential side effects of available drugs. Silodosin is a valid option for elderly and for people taking anti-

hypertensive drugs. They stated that BPH patients affected by ED can target both conditions with continuous tadalafil therapy. The encouraging data on mirabegron use in BPH-DO have to be further assessed in larger prospective RCTs.

Faber et al (2015) evaluated the safety and effectiveness of a novel robotic tissue ablation system (PROCEPT Aquablation™ System), in performing prostate ablation in a survival canine model. This novel technology uses a high-velocity saline stream that aims to selectively ablate prostatic glandular tissue while sparing collagenous structures such as blood vessels and capsule. Once the ablation is complete, a laser beam is captured by a low-pressure water jet to produce surface hemostasis. The extent and depth of ablation is pre-determined by endoscopic and transrectal ultrasonography guidance. The procedure was performed in 8 non-castrated male beagles aged 6 years or older (Acute 2, Chronic 6) through a previously created perineal urethrostomy. Aquablation time ranged from 40 to 84 seconds (mean of 60.5 sec). There was no active bleeding in any of the dogs during or after Aquablation. Water jet-guided laser coagulation was used for purposes of monitoring its safety and effectiveness; 5 of the 6 dogs reached the pre-determined 6-week mark. Complications included 2 dogs with infection successfully treated with antibiotics, a false passage created during catheter placement, and 2 bladder neck perforations (from mechanical insertion), 1 leading to euthanasia. Histologic evaluation at 6 weeks revealed a normal cellular architecture and full re-epithelialization of the treatment cavity. The authors reported the initial survival data in the animal model of a novel robotic device developed for managing symptomatic BPH. They stated that Aquablation produced ablation of adenomatous elements while preserving collagenous structures and is a promising technology for surgical management of symptomatic BPH.

Jones et al (2015) stated that PAE has emerged as a promising treatment for LUTS secondary to BPH. However, although it has gained increasing attention in radiology literature, it remains under-reported from a urologic perspective. These researchers provided an up-to-date review of this minimally invasive technique. Evidence suggests it is a promising and effective option for patients with large prostate volumes, multiple co-morbidities, and suboptimal results from pharmacotherapy. The authors

concluded that larger, randomized studies with longer follow-up periods are needed for this technique to be formally established in the urology community.

Lebdai et al (2016) reviewed current knowledge on clinical outcomes and peri-operative complications of PAE in patients treated for LUTS related to BPO. A systematic review of the literature published from January 2008 to January 2015 was performed on PubMed/MEDLINE. A total of 57 articles were identified, and 4 were selected for inclusion in this review. Only 1 RCT compared TURP to PAE. At 3 months after the procedure, mean IPSS reduction from baseline ranged from 7.2 to 15.6 points. Mean urine peak-flow improvement ranged from +3.21 ml/s to +9.5 ml/s. When compared to TURP, PAE was associated with a significantly lower IPSS reduction 1 and 3 months after the procedure. A trend toward similar symptoms improvement was however reported without statistical significance from 6 to 24 months. Major complications were rare with 1 bladder partial necrosis due to non-selective embolization. Mild adverse events occurred in 10 % of the patients and included transient hyperthermia, hematuria, rectal bleeding, painful urination or acute urinary retention. Further comparative studies are mandatory to assess post-operative rates of complications, especially acute urinary retention, after PAE and standard procedures. The authors concluded that early reports suggested that PAE may be a promising procedure for the treatment of patients with LUTS due to BPO. However, the low level of evidence and short follow-up of published reports precluded any firm conclusion on its mid-term efficiency. They stated that further clinical trials are needed before it is used in clinical practice.

Bipolar Plasma Enucleation of the Prostate

Geavlete et al (2013) evaluated the viability of bipolar plasma enucleation of the prostate (BPEP) by comparison with open transvesical prostatectomy (OP) in cases of large prostates with regard to surgical efficacy and peri-operative morbidity. These researchers compared the medium-term follow-up parameters specific for the 2 methods. A total of 140 BPH patients with prostate volume greater than 80 ml, Qmax less than 10 ml/s and IPSS greater than 19 were randomized in the 2 study arms. All cases were assessed pre-operatively and at 1, 3, 6 and 12 months after surgery by IPSS, Qmax , quality of life score (QoL) and

PVR urinary volume. The prostate volume and PSA level were measured at 6 and 12 months. The BPEP and OP techniques emphasized similar mean operating durations (91.4 versus 87.5 mins) and resected tissue weights (108.3 versus 115.4 g). The post-operative hematuria rate (2.9 % versus 12.9 %) as well as the mean hemoglobin drop (1.7 versus 3.1 g/dL), catheterization period (1.5 versus 5.8 days) and hospital stay (2.1 versus 6.9 days) were significantly improved for BPEP. Re-catheterization for acute urinary retention was more frequent in the OP group (8.6 % versus 1.4 %), while the rates of early irritative symptoms were similar for BPEP and OP (11.4 % versus 7.1 %). During the follow-up period, no statistically significant difference was determined in terms of IPSS, Qmax , QoL, PVR, PSA level and post-operative prostate volume between the 2 series. The authors concluded that BPEP represents a promising endoscopic approach in large BPH cases, characterized by good surgical efficiency and similar BPH tissue removal capabilities compared with standard transvesical prostatectomy. They noted that BPEP patients benefited from significantly reduced complications, shorter convalescence and satisfactory follow-up symptom scores and voiding parameters.

da Silva et al (2015) stated that for decades, the monopolar TURP has been established as the minimally invasive surgical treatment for patients with BPH. In recent years, new technologies and devices emerged to reduce the morbidity and improve outcomes for this treatment approach. Bipolar energy introduced the use of saline irrigation and laser technology increased the urological armamentarium to treat BPH. These researchers performed a systematic review of the literature regarding bipolar technology for the treatment of BPH; a Medline database search using the PRISMA methodology was carried out. Selected literature was restricted to articles published in English and published between 2005 and 2015. Articles regarding techniques using bipolar energy were included, while manuscripts that used a different technique, hybrid techniques, or techniques other than bipolar resection, bipolar vaporization, and bipolar enucleation were excluded. The use of bipolar energy in the endoscopic treatment of BPH presented a significant reduction in operative time, peri-operative complications, shorter catheterization time, reduced number of blood products transfused, and shorter hospital stay compared to standard techniques. Post-operative outcomes showed that bipolar energy was safe and offered significant

outcome improvement when compared to traditional monopolar TURP. The authors concluded that the use of bipolar energy in the surgical treatment of patients with BPH is safe and is associated with improvements in peri-operative outcomes. They stated that short- and mid-term functional outcomes were comparable to standard techniques, but long-term functional outcomes need better clinical evaluation.

Histotripsy

Histotripsy is a non-invasive, non-thermal, focused US therapy that mechanically liquefies targeted tissues within the body. It induces a process known as controlled cavitation (formation of microbubbles) within targeted tissues. The microbubbles oscillate back and forth, come together, and collapse in a very precise manner.

Nair and colleagues (2015) stated that LUTS are common and are often caused by BPH. Traditional surgical methods of open enucleation and TURP have been effective in alleviating these symptoms however, these are operator-dependent and often come with significant side effects. These investigators discussed upcoming new surgical techniques in management of BPH. A systematic search of SCOPUS, MEDLINE, EMBASE and Cochrane databases was carried out using relevant key words. Intra-prostatic injections with a variety of agents have been explored as these can be readily performed under local anesthesia. Alcohol injections into the prostate have been abandoned due to potential side effects; but there has been ongoing development of 2 alternative agents, NX-1207 and PRX-302. Both have shown good safety profiles and early effectiveness in phase II studies. Thermal treatment with the Rezūm device performed as an out-patient procedure has shown both safety and effectiveness in phase I and II studies. Aquablation showed promise in phase II studies with few side effects and is a relatively automated procedure, albeit requiring general anesthesia. Prostate artery embolization has been reported in a number of studies, but clinical outcomes have been unpredictable. Histotripsy has had a number of complications in animal models and despite technical improvement has not yet progressed beyond feasibility studies in humans. The authors concluded that some of the new techniques and technologies available for BPH have been shown to be relatively safe and effective and await validation with phase III clinical trials.

Aoun et al (2015) noted that BPH represents a spectrum of related LUTS. The cost of currently recommended medications and the discontinuation rate due to side effects are significant drawbacks limiting their long-term use in clinical practice. Interventional procedures, considered as the definitive treatment for BPH, carry a significant risk of treatment-related complications in frail patients. These issues have contributed to the emergence of new approaches as alternative options to standard therapies. These investigators reviewed the recent literature regarding the experimental treatments under investigation and presented the currently available experimental devices and techniques used under local anesthesia for the treatment of LUTS/BPH in the vast majority of cases. They discussed devices for delivery of thermal treatment (microwaves, radiofrequency, high-intensity focused ultrasound, and the Rezūm system), mechanical devices (prostatic stent and urethral lift), fractionation of prostatic tissue (histotripsy and aquablation), PAE, and intra-prostatic drugs; and analyzed evidence for the safety, tolerability, and efficacy of these "minimally invasive procedures".

Khokhlova et al (2015) stated that in high intensity focused ultrasound (HIFU) therapy, an ultrasound beam is focused within the body to locally affect the targeted site without damaging intervening tissues. The most common HIFU regime is thermal ablation. Recently there has been increasing interest in generating purely mechanical lesions in tissue (histotripsy). These investigators provided an overview of several studies on the development of histotripsy methods toward clinical applications. They presented 2 histotripsy approaches and examples of their applications. In one approach, sequences of high-amplitude, short (microsecond-long), focused ultrasound pulses periodically produce dense, energetic bubble clouds that mechanically disintegrate tissue. In an alternative approach, longer (millisecond-long) pulses with shock fronts generate boiling bubbles and the interaction of shock fronts with the resulting vapor cavity causes tissue disintegration. Recent pre-clinical studies on histotripsy were reviewed for treating BPH, liver and kidney tumors, kidney stone fragmentation, enhancing anti-tumor immune response, and tissue de-cellularization for regenerative medicine applications. Potential clinical advantages of the histotripsy methods were discussed. Histotripsy methods can be used to mechanically ablate a wide variety of tissues, while selectivity sparing structures such as large vessels. Both ultrasound and magnetic resonance imaging (MRI) can be

used for targeting and monitoring the treatment in real time. The authors concluded that although the 2 approaches utilize different mechanisms for tissue disintegration, both have many of the same advantages and offer a promising alternative method of non-invasive surgery.

Phytotherapy

Keehn and Lowe (2015) noted that the use of complementary and alternative medications has become a multi-million dollar business in the United States and comprises more than 50 % of all filled prescriptions for BPH in Europe. For the practicing urologist, understanding the phytotherapeutic agents available, their proposed mechanism of action, the research supporting their use; and their safety profiles has become increasingly important as more patients inquire into their use. A comprehensive literature search was conducted to identify pertinent articles pertaining to alternative and complementary treatment options for the management of BPH. Treatments demonstrating adequate clinical data, including Serona repens (saw palmetto), Pygeum africanum (African plum tree bark) , and Secale cereal (rye pollen), were selected for in depth review. Small clinical trials for each of the agents demonstrated mixed results while larger more soundly constructed studies found no significant benefit for the use of phytotherapy in the treatment of BPH. The authors concluded that based on the available literature, there is no evidence that phytotherapy significantly improves symptoms of BPH against placebo, despite being largely safe for ingestion. They stated that in patients with mild BPH symptoms who are reluctant to take standard pharmaceutical medications may try these agents provided that the patient understands their current limitations. Those with moderate or severe BPH should be discouraged from alternative and complementary treatments.

Furthermore, a Medscape review on "Benign prostatic hypertrophy" (Deters, 2015) states that "Phytotherapeutic agents and dietary supplements are considered emerging therapy by the AUA Guidelines panel and are not recommended for the treatment of BPH because of the lack of evidence at this time". Examples of phytotherapeutic agents are African plum tree bark, pumpkin seeds, rye pollen, saw palmetto, South African star grass roots, and Stinging nettle roots.

The Rezum System (Convective Radiofrequency Transurethral Water Vapor Therapy)

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

Dixon et al (2015) evaluated the acute ablative characteristics of transurethral convective water vapor (steam) using the Rezūm® system in men with BPH through histologic and radiographic studies. A total of 7 patients were treated with transurethral intra-prostatic injections of sterile steam under endoscopic visualization followed by previously scheduled adenectomies. The extirpated adenomas were grossly examined followed by whole mount sectioning and staining with triphenyl-tetrazolium chloride (TTC) to evaluate thermal ablation. Histology was performed after hematoxylin and eosin staining on 1 prostate. After review of results from the first patient cohort, an additional 15 patients with clinical BPH were treated followed by gadolinium-enhanced magnetic resonance imaging (MRI) at 1 week. In the first patient cohort, gross examination of TTC-stained tissue showed thermal ablation in the transition zone. In addition, there was a distinct interface between viable and necrotic prostatic parenchyma. Histopathologic examination revealed TTC staining-outlined necrotic versus viable tissue. Gadolinium-enhanced MRIs in the cohort of 15 patients demonstrated lesion defects in all patients at 1 week post-procedure. Coalesced lesions were noted with a mean (± standard deviation) lesion volume of 9.6 ± 8.5 cm(3). The largest lesion volume was 35.1 cm(3). Ablation using vapor was rapid and remained confined to the transition zone, consistent with the thermodynamic principles of convective thermal energy transfer. The authors concluded that thermal ablation was observed in all specimens. The resulting coalescing ablative lesions, as seen on MRI, were confined

to the transition zone. They stated that these studies confirmed the ablative capabilities of vapor, validated the thermodynamic principles of convective heating, and allowed for further clinical studies.

McVary et al (2016) reported on the results of a multicenter, randomized, controlled study using transurethral prostate convective water vapor thermal energy to treat lower urinary tract symptoms associated with benign prostatic hyperplasia. Men 50 years old or older with an International Prostate Symptom Score of 13 or greater, maximum flow rate of 15 ml per second or less and prostate size 30 to 80 cc were randomized 2:1 between thermal therapy with the Rezūm® System and control. Thermal water vapor was injected into the transition zone and median lobe as needed. The control procedure was rigid cystoscopy with simulated active treatment sounds. The primary end point compared International Prostate Symptom Score reduction at 3 months. Treatment subjects were followed for 12 months. There were 197 men randomized (active 136, control 61). Thermal therapy and control International Prostate Symptom Score was reduced by 11.2 ± 7.6 and 4.3 ± 6.9 respectively ($p < 0.0001$). Treatment subject baseline International Prostate Symptom Score of 22 decreased at 2 weeks (18.6, $p=0.0006$) and by 50% or greater at 3, 6 and 12 months, $p < 0.0001$. The peak flow rate increased by 6.2 ml per second at 3 months and was sustained throughout 12 months ($p < 0.0001$). No de novo erectile dysfunction was reported. Adverse events were mild to moderate and resolved quickly. The investigators concluded that convective water vapor thermal therapy provides rapid and durable improvements in benign prostatic hyperplasia symptoms and preserves erectile and ejaculatory function. Treatment can be delivered in an office or hospital setting using oral pain medication and is applicable to all prostate zones including the median lobe.

McVary and colleagues (2019) reported 4-year outcomes of the RCT of water vapor thermal therapy for the treatment of moderate-to-severe lower urinary tract symptoms due to BPH. A total 188 subjects; 135 men greater than or equal to 50 years of age, IPSS greater than or equal to 13, Qmax less than or equal to 15 ml/s and prostate volume of 30 to 80 cc treated with the Rezūm System thermal therapy were followed for 4 years; subset of 53 men who re-qualified for cross-over from control to active treatment were followed for 3 years. Lower urinary tract symptoms were significantly improved within 3 months or less following thermal

therapy and remained consistently durable (IPSS 47 %, QOL 43 %, Qmax 50 %, Benign Prostatic Hyperplasia Impact Index 52 %) throughout 4 years ($p < 0.0001$); outcomes were similarly sustained in cross-over subjects at 3 years. Surgical re-treatment rate was 4.4 % over 4 years. No disturbances in sexual function were reported. The authors concluded that minimally invasive thermal therapy provided effective symptom relief and improved QOL that remained durable for over 4 years. It is applicable to all prostate zones with procedures performed under local anesthesia in an office setting. These researchers stated that the procedure has a minimal physician learning curve and early intervention with this thermal therapy rather than use of pharmaceutical agents or invasive surgery may be an ideal option for men with moderate-to-severe LUTS at risk for BPH progression.

Guidelines from the AAUA (Foster et al, 2019) stated that "Water vapor thermal therapy may be offered to patients with LUTS attributed to BPH provided prostate volume < 80 g; however, patients should be counseled regarding efficacy and retreatment rates". The guidelines stated that "Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function". These were "conditional recommendations" based upon evidence about which the panel has a low level of certainty (evidence level Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data)).

Miller and colleagues (2020) performed a systematic review and meta-analysis of studies utilizing water vapor thermal therapy (WVTT) for the treatment of symptomatic BPH. The IPSS, IPSS-QOL, BPH impact index (BPHII), and Qmax were calculated as the weighted mean difference relative to baseline and reported in minimal clinically important difference (MCID) units. MCID thresholds were -3 for IPSS, -0.5 for IPSS-QOL, -0.5 for BPHII, and 2 ml/s for Qmax. The surgical re-treatment rate was calculated using life-table methods. These investigators identified 5 cohorts treated with WVTT from 4 studies (514 patients; 40 % with median lobe obstruction) with 2 years median follow-up (range of 6 months to 4 years). The IPSS, IPSS-QOL, BPHII, and Qmax significantly improved at all intervals between 3 months and 4 years; this benefit

ranged from 3.3 to 3.8 MCID units for IPSS, 3.9 to 4.6 MCID units for IPSS-QOL, 6.8 to 8.2 MCID units for BPHII, and 1.5 to 3.0 MCID units for Qmax. The surgical re-treatment rate was 7.0 % at 4 years of follow-up data. Most AEs were not serious and transient; dysuria, urinary retention, and urinary tract infection (UTI) were most common. No cases of de-novo ED occurred. The authors concluded that WVTT provided improvement in BPH symptoms that exceeded established MCID thresholds, preserved sexual function, and was associated with low surgical re-treatment rates over 4 years. These researchers stated that these findings suggested that the WVTT procedure may be a valuable addition to the urological armamentarium to treat LUTS in men with BPH.

The authors stated that this meta-analysis had several drawbacks. First, there was less precision in the results with extended follow-up since fewer studies with longer term data were available. Additional studies would improve the reliability of the meta-analysis estimates. Second, the number of included studies was insufficient to evaluate publication bias or sources of heterogeneity. Third, patients in the included studies typically presented with a prostate volume no larger than 80 cc and, therefore, the safety and effectiveness of WVTT in larger prostates were unclear. A clinical trial of WVTT for prostate sizes between 80 and 150 cc is ongoing, but results are not yet unavailable. Fourth, retrospective enrollment, unclear inclusion criteria, and limited follow-up duration were aspects of certain studies that may limit interpretability of results. Fifth, AE reporting was inconsistent among studies and it was unclear if complication under-reporting may have affected the accuracy of the estimates. Development of consistent and comprehensive AE reporting standards for use in future trials of minimally invasive BPH therapies is needed. Finally, although 1 study utilized a sham control, most control patients elected to cross-over to WVTT at 3 months due to insufficient symptom relief. Aside from this 3-month period in a single study, direct comparative data with a control group or other BPH treatments are not available. Therefore, comparisons of results with WVTT versus treatments such as PUL or TURP should be interpreted cautiously.

Kang and colleagues (2020) stated that new minimal invasive surgeries have been suggested as alternative options to TURP for the management of LUTS in men with BPH. Convective radiofrequency water vapor thermal therapy (RF-WVTT) is a new technology that uses targeted,

controlled water vapor energy (steam) to create necrotic tissue in the prostate. In a Cochrane review, these investigators examined the effects of convective RF-WVTT for the treatment of LUTS in men with BPH. These researchers carried out a comprehensive search of multiple data-bases (the Cochrane Library, Medline, Embase, Latin American and the Caribbean Health Sciences Literature, Scopus, Web of Science), trials registries, other sources of grey literature, and conference proceedings published up to February 18, 2020, with no restriction on the language or status of publication. They included parallel-group RCTs, cluster-RCTs, and non-randomized observational prospective studies with concurrent comparison groups, in which men with BPH underwent convective RF-WVTT, another active therapy, or a sham procedure. Two review authors independently screened the literature, extracted data, and assessed risk of bias. They had planned to perform statistical analyses using a random-effects model, and interpret them according to the Cochrane Handbook for Systematic Reviews of Interventions. They rated the certainty of the evidence according to the GRADE approach.

These researchers included a single, industry-sponsored RCT, with 197 randomized men, that compared convective RF-WVTT to a sham procedure. The mean age 62.9 years, the IPSS was 21.97, and the mean PV was 45.4 ml. They only found short-term data, measured up to 3 months; and found convective RF-WVTT may improve urologic symptom scores more than a sham procedure, measured on a IPSS scale (0 to 35; higher score represents worse urological symptoms) by a MD of -6.9 (95 % CI: -9.06 to -4.74; 195 men; low-certainty evidence), and likely improves QOL, measured on a IPSS-QOL scale (0 to 6; higher score represents worse QOL), by a MD of -1.2 (95 % CI -1.66 to -0.74; 195 men; moderate-certainty evidence). These investigators were very uncertain about the effects of convective RF-WVTT on major AEs (RR 6.79, 95 % CI: 0.39 to 117.00; 197 men; very low-certainty evidence) assessed by the Clavien-Dindo classification system of III, IV, and V complications. These researchers were also very uncertain about the effects of convective RF-WVTT on re-treatment (RR 1.36, 95 % CI: 0.06 to 32.86; 197 men; very low-certainty evidence). Convective RF-WVTT may have little to no effect on erectile function (MD 0.4, 95 % CI: -1.91 to 2.71; 130 men; low-certainty evidence) and ejaculatory function (MD 0.5, 95 % CI: -0.83 to 1.83; 130 men; low-certainty evidence). Convective RF-WVTT may increase minor AEs assessed by the Clavien-Dindo

classification system of grade I and II complications (RR 1.89, 95 % CI: 1.15 to 3.11; 197 men; low-certainty evidence). This would correspond to 434 minor AEs/1,000 men (95 % CI: 264 more to 714 more). These researchers were very uncertain about the effects of convective RF-WVTT on acute urinary retention (RR 4.98, 95 % CI: 0.28 to 86.63; 197 men; very low-certainty evidence). It likely greatly increased the rate of men requiring indwelling urinary catheters (RR 35.58, 95 % CI: 15.37 to 82.36; 197 men; moderate-certainty evidence). These investigators were unable to perform any of the pre-defined secondary analyses. Moreover, they found no evidence for other comparisons, such as convective RF-WVTT versus TURP or other minimal invasive procedures.

The authors concluded that compared to a sham procedure, urologic symptom scores and QOL appeared to improve with convective RF-WVTT, however, they were very uncertain regarding major AEs. The certainty of evidence ranged from moderate-to-very low, with study limitations and imprecision being the most common reasons for rating down. These findings were based on a single industry-sponsored study, with 3-month short-term follow-up. These researchers did not find any studies comparing convective RF-WVTT to any other active treatment form, such as TURP.

Botulinum Toxin Injection

Alam and associates (2016) described the case of a 75-year old male patient with a chronic history of obstructive LUTS and multiple co-morbidities who was admitted to the hospital for management of recurrent urinary retention. The patient was not a surgical candidate for TUIP or TURP. Botulinum toxin injection into the bladder neck was performed with very satisfying results. The authors concluded that BTX injection in the bladder neck presents a promising minimally invasive, tolerated, and cost-effective approach for the treatment of urinary retention in patients with BPO who are not candidates for surgery or in whom medical treatment has failed. They stated that more research is needed to identify the effectiveness of this novel approach.

Shim and colleagues (2016) examined the safety and effectiveness of botulinum toxin type A (BTX-A) compared with placebo for the treatment of BPH. These researchers conducted a systematic review and meta-

analysis of the published literature in PubMed, Cochrane Library, and Embase reporting on BTX use in LUTS/ BPH. Single-group analysis for the placebo effect and meta-regression analysis for the moderator effect were performed with high-quality RCTs compared with placebo. A total of 3 studies were included, with a total sample size of 522 subjects (260 subjects in the experimental group and 262 subjects in the control group). Study duration ranged from 8 to 24 weeks. The pooled overall standardized mean difference (SMD) in the mean change in IPSS for the BTX-A group versus the placebo group was -1.02 (95 % confidence interval [CI]: -1.97, -0.07). The other outcomes (Qmax, prostate volume, and PVR volume) were not statistically different between the 2 groups. The placebo effect in single-group analysis ranged from 0 to 27.9 % for IPSS, and from -1.1 to 28.7 % for Qmax (lowest to highest, respectively). The authors concluded that this evidence-based systematic review and meta-analysis of the BTX-A injection for LUTS/BPH showed no differences in the effectiveness compared with placebo and also showed no difference in procedure-related adverse events occurred. Thus, the results of this study did not provide evidence of clinical benefits of using the BTX-A injection for LUTS/BPH in real clinical practice.

Transurethral Thulium Laser Ablation

Zhu and colleagues (2015) evaluated the safety and effectiveness of thulium laser versus standard TURP for treating patients with BPO. These investigators performed a systematic search of the electronic databases, including Medline, Embase, Web of Science, and the Cochrane Library, up to February 1, 2014. The pooled estimates of demographic and clinical baseline characteristics, peri-operative variables, complications, and post-operative effectiveness including IPSS, QOL, Qmax, and PVR were calculated. A total of 7 trials assessing thulium laser versus standard TURP were considered suitable for meta-analysis including 4 RCTs and 3 non-RCTs. Compared with TURP, although thulium laser prostatectomy (TmLRP) needed a longer operative time [weighted mean difference (WMD) 8.18 min; 95 % CI: 1.60 to 14.75; p = 0.01], patients having TmLRP might benefit from significantly less serum sodium decreased (-3.73 mmol/L; 95 % CI: -4.41 to -3.05; p < 0.001), shorter time of catheterization (WMD -1.29 days; 95 % CI: -1.95 to -0.63; p < 0.001), shorter length of hospital stay (WMD -1.83 days; 95 % CI: -3.10 to -0.57; p = 0.005), and less transfusion (odds ratio [OR] 0.09;

95 % CI: 0.02 to 0.41; p = 0.002). During the 1, 3, and, 12 months of post-operative follow-up, the procedures did not demonstrate a significant difference in IPSS, QOL, Qmax, and PVR. The authors concluded that TmLRP had a similar efficacy to standard TURP in terms of IPSS, QOL, Qmax, and PVR, and offered several advantages over TURP in terms of blood transfusion, serum sodium decreased, catheterization time, and hospital stay, while TURP was superior in terms of operation duration. Moreover, they stated that well-designed multi-centric/international RCTs with long-term follow-up are still needed.

Zhang et al (2016) stated that all available surgical treatments for BPH have their individual advantages or disadvantages. However, the lack of head-to-head studies comparing different surgeries makes it unavailable to conduct direct analysis. To compare the safety and effectiveness among different lasers and TURP for BPH, RCTs were searched in Medline, Embase, Cochrane library, WHO International Clinical Trial Registration Platform, and Clinical Trial.gov by May 2015; and the effectiveness-, perioperation- and complication-related outcomes were assessed by network meta-analysis. A total of 36 studies involving 3,831 patients were included. Holmium laser through resection and enucleation had the best efficacy in Qmax. Thulium laser through vapo-resection was superior in improving IPSS and holmium laser through enucleation was the best for PVR volume improvement. Diode laser through vaporization was the rapidest in removing post-operative indwelling catheter, while TURP was the longest; TURP required the longest hospitalization and thulium laser through vapo-resection was relatively shorter. The authors concluded that holmium and thulium lasers appeared to be relatively better in surgical safety and effectiveness, so that these 2 lasers might be preferred in selection of optimal laser surgery. However, they stated that more large-scale and high quality head-to-head RCTs are needed to validate the conclusions.

Marra and associates (2016) noted that although ejaculatory dysfunction is common for patients undergoing BPH surgery, no clear evidence is present to counsel patients seeking to preserve ejaculatory function. These investigators evaluated ejaculatory dysfunction in relation to BPH surgery. They carried out a Web and manual search using Medline and Embase including RCTs reporting ejaculatory dysfunction after BPH surgery: 42 RCTs comprising a total of 3,857 patients were included.

Only 1 study had ejaculatory dysfunction as a primary outcome, and just 10 evaluated ejaculatory dysfunction before and after surgery. The definition of ejaculatory dysfunction was not standardized. Similarly, just 7 studies used internationally validated questionnaires to address ejaculatory dysfunction. The reported rates of ejaculatory dysfunction after resectional electro-surgery, laser procedures, coagulation, ablation and implant techniques were assessed and compared. Transurethral resection of the prostate and recent laser procedures including holmium, thulium and GreenLight caused similar rates of ejaculatory dysfunction, occurring in almost 3 out of 4 to 5 men. Although providing less symptomatic benefit compared with TURP, transurethral incision of the prostate, TUNA and TUMT should be considered for men aiming to maintain normal ejaculation. UroLift is also a recent promising option for this category of patients. The authors concluded that the vast majority of studies reporting ejaculatory dysfunction after BPH surgery used poor methodology to investigate this complication. They stated that future studies able to address clear hypothesis and considering ejaculatory dysfunction anatomical and pathophysiological features are needed to develop ejaculation preserving techniques and to increase the evidence to counsel men aiming to preserve ejaculation.

Li et al (2016) noted that LUTS/ BPH is common in adult men and can impair erectile function (EF). It was believed surgical treatments for this illness can improve EF due to the relief of LUTS while they were also reported harmed EF as heating or injury effect. Current network meta-analysis aimed to elucidate this discrepancy; RCTs were identified. Direct comparisons were conducted by STATA and network meta-analysis was conducted by Generate Mixed Treatment Comparison. Random-effects models were used to calculate pooled SMD and 95 % CIs and to incorporate variation between studies. A total of 18 RCTs with 2,433 subjects were analyzed; 9 approaches were studied: TURP, plasmakinetic resection of the prostate (PKRP), plasmakinetic enucleation of the prostate (PKEP), holmium laser enucleation of the prostate (HoLEP), holmium laser resection of the prostate (HoLRP), photoselective vaporization of the prostate (PVP), Thulium laser, open prostatectomy (OP), and laparoscopic simple prostatectomy (LSP). In direct comparisons, all surgical treatments did not decrease post-operative IIEF-5 score except PVP. Moreover, patients who underwent HoLEP, PKEP, Thulium laser, and TURP had their post-operative EF

significantly increased. Network analysis including direct and indirect comparisons ranked LSP at the highest position on the variation of post-operative IIEF-5 score, followed by PKRP, HoLEP, TURP, Thulium laser, PKEP, PVP, HoLRP, and OP. In subgroup analysis, only PVP was found lower post-operative EF in the short-term and decreased baseline group, whereas TURP increased post-operative IIEF-5 score only for patients with normal baseline EF. However, HoLEP and PKEP showed pro-erectile effect even for patients with decreased baseline EF and short-term follow-up. The authors concluded that their novel data demonstrating surgical treatments for LUTS/BPH showed no negative impact on post-operative EF except PVP. Moreover, HoLEP and PKEP were found pro-erectile effect for all subgroups. New technologies, such as LSP, PKRP, and Thulium laser, were ranked at top positions in the network analysis, although they had no pro-erectile effect in direct comparison due to limited original studies or poor baseline EF. They stated that further studies and longer follow-up are needed to substantiate these findings.

Feng et al (2016) compared the safety and effectiveness of thulium laser enucleation of the prostate (ThuLEP) with PKEP. A total of 127 patients with BPH were randomized to either ThuLEP (n = 61) or PKEP (n = 66). All patients were assessed pre-operatively and followed-up at 3, 6, and 12 months post-operatively. Baseline characteristics of the patients, peri-operative data, post-operative outcomes, and complications were recorded. The decrease in hemoglobin level and the catheter time were statistically significantly lower in the ThuLEP group compared with the PKEP group (0.80 ± 0.49 versus 0.99 ± 0.52, p = 0.037, and 1.85 ± 0.94 versus 2.28 ± 1.34, p = 0.042). There were no statistical differences in complications between the 2 groups (p > 0.05). There was a significant improvement in 3, 6, and 12 months' parameters compared with pre-operative values (p < 0.001). Assessment at the 12-month follow-up showed no difference in urinary parameters between the 2 groups. The authors concluded that ThuLEP and PKEP are both safe and efficient procedures for the treatment of patients with BPH. Compared with PKEP, ThuLEP provided less risk of hemorrhage and shorter catheter time, although the differences may be of little clinical relevance. Moreover, they stated that further well-designed trials with extended follow-up and larger sample size are needed to draw final conclusions about the effectiveness of these 2 procedures.

Rieken et al (2016) stated that surgical techniques are an integral part of the urologist's armamentarium for the treatment of BPO. Currently, several techniques are available. These investigators analyzed the long-term outcomes of currently available techniques. Open prostatectomy shows a low long-term re-operation rate. Available evidence suggests that bi-polar TURP is an attractive alternative to mono-polar TURP as both techniques lead to a long-lasting and comparable efficacy. For patients with a larger prostate volume, bi-polar enucleation of the prostate appears as safe and effective alternative to open prostatectomy. Holmium laser enucleation of the prostate appears as a durable alternative to TURP and open prostatectomy with comparable long-term results. For photo-selective vaporization of the prostate, differently powered models are available. Currently, only long-term data with lower powered 80 W laser are available, reporting re-operation rates higher than those reported from other surgical techniques. The authors noted that on the thulium laser, currently only 1 study reported 5-year results and despite encouraging results further confirmation seems necessary.

In a meta-analysis, Zhao et al (2016) compared the safety and effectiveness of thulium laser resection of prostate (ThuRP) and PKRP for BPH. A systematic search of PubMed, Web of Science, and China National Knowledge Infrastructure was performed up to October 1, 2015. Outcomes of interest assessing the 2 techniques included demographic and clinical characteristics, peri-operative variables, follow-up data, and complications. A total of 9 eligible trials evaluating ThuRP versus PKRP for BPH were identified, including 6 RCTs and 3 retrospective trials. ThuRP was associated with longer operation time ($p < 0.001$), shorter hospital stay ($p < 0.001$), irrigation ($p = 0.02$), and catheterization ($p < 0.001$) duration. Estimated blood loss ($p = 0.005$) and drop in hemoglobin level ($p = 0.02$) were significantly more in PKRP. Except QOL score ($p = 0.04$), which was better in ThuRP, the post-operative data, including IPSS ($p = 0.44$), Qmax ($p = 0.33$), PVR urine volume ($p = 0.55$), and the complications such as severe bleeding ($p = 0.52$), temporary urinary retention ($p = 0.20$), temporary urinary incontinence ($p = 0.64$), urinary tract infection ($p = 0.83$), and urethral stricture ($p = 0.22$), did not differ significantly. The authors concluded that their analysis showed that there was no significant difference in terms of effectiveness between ThuRP and PKRP. Although ThuRP was associated with longer operation time, it

possessed more safe capacity with less blood loss, shorter hospital stay, irrigation, and catheterization duration. They stated that more worldwide RCTs with long-term follow-up are still needed to support their conclusion.

Zhuo et al (2017) noted that the 2-μm thulium laser resection of the prostate-tangerine technique (TmLRP-TT) has been introduced as a minimally invasive treatment for BPH. These researchers evaluated the safety and effectiveness of TmLRP-TT for the treatment of BPH patients with previously negative trans-rectal prostate biopsy. A prospective analysis of 51 patients with previously negative trans-rectal prostate biopsy who underwent surgical treatment using TmLRP-TT was performed from December 2011 to December 2013. Pre-operative status, surgical details, and peri-operative complications were recorded. The follow-up outcome was evaluated with subjective and objective tests at 1 and 6 months; TmLRP-TT was successfully completed in all patients. Mean prostate volume, operative duration, and catheterization time were 93.3 ± 37.9 ml, 69.5 ± 39.5 mins, and 6.5 ± 1.3 days, respectively. The mean IPSS, QOL score, Qmax, and PVR urine volume changed notably at 6-month follow-up (22.5 ± 6.9 versus 6.1 ± 3.2, 4.8 ± 1.3 versus 1.1 ± 0.9, 7.3 ± 4.5 versus 18.9 ± 7.1 ml s-1 , and 148.7 ± 168.7 versus 28.4 ± 17.9 ml). Two (3.9 %) patients required blood transfusion peri-operatively, while 3 (5.9 %) patients experienced transient hematuria post-operatively, and 2 (3.9 %) patients received 3 days re-catheterization due to clot retention. The authors concluded that TmLRP-TT is a safe and effective minimally invasive technique for patients with previously negative trans-rectal prostate biopsy during the 6-month follow-up. They stated that this promising technology may be a feasible surgical method for previously negative trans-rectal prostate biopsy in the future.

Tests for Diagnostic Evaluation for BPH

An UpToDate review on "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia" (Cunningham and Kadmon, 2017) states that "Most patients with benign prostatic hyperplasia (BPH) do not require additional testing. However, other studies may be useful in selected cases. These include urinary cytology (if bladder cancer is a concern), genitourinary ultrasonography (for evaluation of renal dysfunction or urinary tract infection), post-void residual volume (if urinary retention is a

concern and prior to initiation of an anticholinergic drug), and urethrocystoscopy (for urethral stricture, bladder calculi, and bladder cancer). Other studies, including maximal urinary flow rate, pressure-flow studies, and prostate ultrasonography, are seldom indicated".

Seldom indicated studies – These studies, which are not usually necessary in patients with BPH, may occasionally be requested or performed by a urologist:

Prostate ultrasonography – Despite the fact that BPH often differentially occurs in the central or transitional zone of the prostate, ultrasound measurements of central zone volume do not appear to correlate better with lower urinary tract symptoms (LUTS) than measurements of total prostate volume . Total prostate volume can be measured by ultrasonography to assess disease progression, and it may be useful in selected patients when considering medical treatment with a 5-alpha-reductase inhibitor (e.g., finasteride), which reduces the size of the prostate gland, or if planning surgery. When prostate volume was compared with enucleated prostate weight in men with BPH undergoing open prostatectomy, transrectal ultrasonography slightly underestimated volume by 4.4 % (95 % CI: 1.7-10.5), whereas transabdominal ultrasonography over-estimated volume by 55.7 % (95 % CI: 31.8-79.6). This information may be helpful in interpreting different types of ultrasound in order to determine which patients should have open prostatectomies.

Maximal urinary flow rate – Maximal urinary flow rate is performed by having the patient void into a collecting device shaped like a cone which has a flow meter embedded into its bottom. The report contains the following information: volume voided, peak and mean flow rates, and a graph of flow in ml/sec as a function of time. To reduce the variability in flow rates, the voided volume should be more than 150 ml. A pre-void bladder volume of > 250 ml with a bladder scan can help to insure that the void volume is > 150 ml. Maximal urinary flow rates > 15 ml/sec are thought to exclude clinically important bladder outlet obstruction. Maximal flow rates < 15 ml/sec are compatible with obstruction from prostatic or urethral disease; however, this finding is not diagnostic since a low flow rate can also result from bladder decompensation. In one study that included 3,140 men who with no or minimal LUTS, 54 % had a peak flow

rate < 15 ml/sec. However, a peak flow rate < 10 ml/sec was associated with an increased likelihood of incident LUTS (HR 1.44, 95 % CI: 1.09-1.91).

Pressure-flow studies – Measurement of the pressure in the bladder during voiding provides the most accurate means for determining bladder outlet obstruction; however, this test requires either transvesical or transurethral insertion of a catheter into the bladder. In a study of 108 men with obstructive symptoms in whom urine flow rates were measured and pressure-flow studies done, only 3 % of those with maximal flow rates below 12 ml/sec were misclassified. This test is usually reserved for men with urinary symptoms and maximal flow rates above 15 ml/sec and those for whom the clinical manifestations are atypical and there is reason to suspect an alternative diagnosis.

Prostatic Artery Embolization for the Treatment of Benign Prostatic Hypertrophy

Kurbatov and associates (2014) examined the safety and benefits of PAE in patients with prostate volume greater than or equal to 80 cm(3) and Charlson co-morbidity index (CCI) greater than or equal to 2 and affected by BPO. From January 2009 to January 2012, PAE was performed in 88 consecutive patients affected by clinical BPO. Inclusion criteria were symptomatic BPO refractory to medical treatment, IPSS greater than or equal to 12, TPV greater than or equal to 80 cm(3), Qmax less than 15 ml/s, and CCI greater than or equal to2. Primary end-points were the reduction of 7 points of the IPSS and the increase of Qmax. Secondary end-points were the reduction of TPV, PVR, PSA, IIEF 5 score, and IPSS-QOL. Follow-up was addressed at 3 months, 6 months, and at 1 year. The mean IPSS (10.40 versus 23.98; $p < 0.05$) and the mean Qmax (16.89 versus 7.28; $p < 0.05$) at 1 year were significantly different with respect to baseline. When considering secondary end-points, these researchers observed significant variation in terms of PVR (18.38 versus 75.25; $p < 0.05$), TPV (71.20 versus 129.31; $p < 0.05$), and PSA level (2.12 versus 3.67; $p < 0.05$) at 1 year compared with baseline. Finally, the mean IPSS-QOL significantly changed from baseline to 1 year after PAE (5.10 versus 2.20; $p < 0.05$). No minor or major complications were reported. The authors showed clinical benefits of PAE for the treatment of LUTS and/or BPO by reducing IPSS, TPV, PSA, PVR, and

improvement in urinary flow and QOL after 1 year in patients with PV greater than or equal to 80 cm(3) and CCI greater than or equal to 2. Moreover, these researchers stated that further comparative studies with other minimally invasive surgical therapies and pathological analysis of prostate specimens are needed to better understand the of PAE efficacy.

The authors stated that this study had 2 main drawbacks. First, this was a single-center study with 1-year follow-up. Second, these investigators did not carry out a match-pair comparison with open prostatectomy or holmium laser enucleation of the prostate (HoLEP) that could have offered an important contribution in understanding the significant benefits of PAE.

In a prospective, single-center, single-arm study, de Assis and colleagues (2015) reported the safety and efficacy of PAE with spherical microparticles to treat LUTS associated with BPH in patients with PV greater than 90 g. This trial was conducted in 35 patients with PV ranging from 90 to 252 g. Mean patient age was 64.8 years (range of 53 to 77); MRI, uroflowmetry, and the IPSS were used to assess clinical and functional outcomes. Mean prostate size decreased significantly from 135.1 g before PAE to 91.9 g at 3 months of follow-up ($p < 0.0001$). Mean IPSS and QOL index improved from 18.3 to 2.7 and 4.8 to 0.9 ($p < 0.0001$ for both), respectively. A significant negative correlation was observed between PSA at 24 hours after PAE and IPSS 3 months after PAE ($p = 0.0057$). The authors concluded that PAE was a safe and effective treatment for LUTS secondary to BPH in patients with PV greater than 90 g. Excessively elevated PSA within 24 hours of PAE was associated with lower symptom burden in short-term follow-up. Moreover, these researchers stated that further analysis of a larger patient population with more extensive follow-up is needed to evaluate PAE in patients with larger prostates more thoroughly. They stated a rigorous, controlled design is needed to compare objectively outcomes after PAE with surgical procedures such as open prostatectomy (OP) and HoLEP.

The authors stated that this study had several drawbacks. This was a single-center study; and the sample size was small (n = 35). Most of the subjects had not yet completed the follow-up, thus these researchers were unable to comment on the mid-term and long-term outcomes of PAE in this population.

Uflacker et al (2016) carried out a meta-analysis of available data on PAE for the treatment of BPH. Meta-analysis was conducted on articles published between November 2009 and December 2015. Peer-reviewed studies with greater than 5 patients and standard deviations and/or individual-level data on 1 or more of the following outcomes were included: PV, Qmax, PVR, IPSS, QOL score, IIEF score, and PSA level. A random-effects meta-analysis was performed on the outcomes at 1, 3, 6, and 12 months after PAE compared with baseline values, with a $p < 0.05$ decision rule as the null hypothesis rejection criterion. A total of 19 of 268 studies were included in data collection, with 6 included in the meta-analysis. At 12 months, PV decreased by 31.31 cm3 ($p < 0.001$), PSA remained unchanged ($p = 0.248$), PVR decreased by 85.54 ml ($p < 0.001$), Qmax increased by 5.39 ml/s ($p < 0.001$), IPSS improved by 20.39 points ($p < 0.001$), QOL score improved by -2.49 points ($p < 0.001$), and IIEF was unchanged ($p = 1.0$). There were a total of 218 AEs among 662 patients (32.93 %), with 216 being Society of Interventional Radiology class A/B (99 %). The most common complications were rectalgia/dysuria (n = 60; 9.0 %) and acute urinary retention (n = 52; 7.8 %). No class D/E complications were reported. The authors concluded that PAE provided improvement in Qmax, PVR, IPSS, and QOL end-points at 12 months, with a low incidence of serious AEs (0.3 %), although minor AEs were common (32.93 %). There was no adverse effect on erectile function. These researchers stated that the findings of this study emphasized the need for higher-quality data reporting, and may serve as a basis for constructing high-quality prospective, replicative studies.

The authors stated that this analysis also highlighted the need for consistent reporting among PAE studies, minimizing redundant data reporting, and the need for prospective, consistent data collection, even at feasibility phases. As noted, even though the authors identified 19 studies that matched their criteria for data collection, only 6 were suitable to be included in the meta-analysis. The 12 excluded studies included overlapping data, lack of standard deviations (SDs), and other missing descriptors and data. Unfortunately, the absence of SDs in PAE results was the norm, making high-level analysis of potentially valuable data impossible -- unless the original authors were willing to impute data, provide individual-level data, or calculate SDs themselves. Another major drawback was the inability to perform paired data analysis, and the

reliance on analyses that compare heterogeneous populations across each study time period of data collection. Stated another way, all currently available PAE studies possess notable drop-offs in study populations overtime.

In a retrospective, single-center, cohort study, Pisco et al (2016a) examined the efficacy of PAE in patients with BPH, PV greater than 100 cm(3). Between March 2009 and September 2014, PAE was carried out in patients with a diagnosis of BPH, PV greater than 100 cm(3), and moderate-to-severe LUTS refractory to medical treatment for at least 6 months or who had acute urinary retention. Success was defined as improved symptoms (IPSS less than or equal to 15 and decrease of greater than or equal to 25 % from baseline score), improved QOL (measured as score of less than or equal to 3 points or decrease of greater than or equal to 1 point from baseline), and no need for additional treatment. PAE was performed in 152 patients aged 48 to 87 years (mean ± SD 67.4 ± 7.5) with mean PV of 134.2 cm(3) ± 41.8 (range of 101 to 383 cm(3)). PAE was technically successful in 149 patients (98.0 %). Symptomatic control was achieved for a median of 18 months ± 15.5 (range of 3 to 66). There were 33 clinical failures (23.6%); 23 occurred in the short-term (less than or equal to 6 months), and 10 occurred in the medium-term (6 to 24 months); there were no long-term failures (greater than 36 months). Cumulative clinical success rates were 90 %, 87.9 %, 83.5 %, 81.1 %, and 77.8 % at 1, 3, 6, 12, and 18 months and 72.4 % thereafter to 66 months (5.5 years). The authors concluded that PAE provides sustained short-, medium-, and long-term control for LUTS in patients with BPH and PV greater than 100 cm(3).

The authors stated that this study had several drawbacks. It was a retrospective, non-randomized, single-center study without a control group. In addition, these investigators did not make any comparisons of different embolic agents or size, and they did not compare PAE with medical or surgical therapies for large prostates. They stated that these are issues that needed to be addressed in future studies.

Pisco et al (2016b) confirmed that PAE has a positive medium- and long-term effect in the treatment of symptomatic BPH. Between March 2009 and October 2014, a total of 630 consecutive patients with BPH and moderate-to-severe LUTS refractory to medical therapy for at least 6

months or who refused any medical therapy underwent PAE. Outcome parameters were evaluated at baseline; 1, 3, and 6 months; every 6 months between 1 and 3 years; and yearly thereafter up to 6.5 years. Mean patient age was 65.1 years ± 8.0 (range of 40 to 89). There were 12 (1.9 %) technical failures. Bilateral PAE was performed in 572 (92.6 %) patients and unilateral PAE was performed in 46 (7.4 %) patients. The cumulative clinical success rates at medium- and long-term follow-up were 81.9 % (95 % CI: 78.3 % to 84.9 %) and 76.3 % (95 % CI: 68.6 % to 82.4 %). There was a statistically significant ($p < 0.0001$) change from baseline to last observed value in all clinical parameters: IPSS, QOL, PV, PSA, Qmax, PVR, and IIEF. There were 2 major complications without sequelae. The authors concluded that PAE had a positive effect on IPSS, QOL, and all objective outcomes in symptomatic BPH. The medium- (1 to 3 years) and long-term (greater than 3 to 6.5 years) clinical success rates were 81.9 % and 76.3 %, with no UI or sexual dysfunction reported. Moreover, these researchers stated that a randomized, placebo-controlled trial is needed to confirm the therapeutic value of PAE.

The authors stated that this study had several drawbacks. It was a non-randomized, single-center study and several subjects were lost to follow-up, either after a first or a second PAE. The number of subjects treated varied with each type of embolic agent because only a few patients were treated with some types, thus results from different types of embolic agents could not be compared. Furthermore, there was no control group of patients undergoing other BPH therapies for comparison.

Cizman et al (2016) reviewed the available safety and efficacy data for PAE in the treatment of BPH. PubMed was searched for publications that included PAE for the treatment of BPH through May 2015; 2 independent reviewers determined the appropriateness for inclusion of each article and compiled data by using pooled weighted means and standard deviations. The literature search identified 161 articles, of which 7 studies, with a total of 562 patients, met all inclusion/exclusion criteria. PAEs were performed bilaterally in 85 % of patients, unilaterally in 12 %, and unsuccessfully in 3 %; IPSS decreased from 24.51 ± 6.12 at baseline to 10.42 ± 5.39 at 6 months; QOL score decreased from 4.76 ± 0.98 at baseline to 2.51 ± 1.13 at 6 months; Qmax increased from 8.41 ml/s ± 2.63 at baseline to 15.44 ml/s ± 5.64 at 6 months; PVR measurement decreased from 105.94 ml ± 76.77 at baseline to 39.57 ml ± 15 at 6

months; PSA level decreased from 4.79 ng/ml ± 5.42 at baseline to 3.16 ng/ml ± 1.5 at 6 months. None of these parameters showed clinically significant changes from 6 months to 12 months; TPV decreased from 96.56 cm3 ± 35.47 at baseline to 46.73 cm3 ± 20.51 at 12 months. There were 200 minor complications and 1 major complication. The authors concluded that PAE improved LUTS caused by BPH, with a favorable short- to mid-term safety profile.

These researchers stated that there are many unanswered questions regarding PAE as a treatment for symptomatic BPH. Future studies should include clear and uniform inclusion and exclusion criteria, sample size calculations, and availability of complete data-sets for future analysis. Future investigations should target RCTs comparing PAE versus TURP or its alternatives. Further research is also needed on the durability of unilateral versus bilateral PAE.

Teoh and colleagues (2017) systemically reviewed the current evidence on (PAE in treating men with BPH. These researchers performed a systemic literature search in PubMed, Embase and Web of Science on May 1, 2016 without time constraints. Outcomes of interest included the changes in the IPSS, QOL score, Qmax, PVR, IIEF score, PV and PSA level. A total of 987 records were identified through database searching. After removing duplicates, screening and reviewing full-length texts, a total of 5 records remained, with 2 RCTs and 3 non-RCTs. Transurethral resection of prostate resulted in better IPSS than PAE. Open prostatectomy had better IPSS, QOL score, Qmax and PVR, but worse IIEF score than PAE at 1 year. Unilateral PAE had higher rate of poor clinical outcome than bilateral PAE, but the difference became statistically insignificant after adjusting for age; IPSS, QOL score, Qmax, PVR, IIEF score, PV and PSA did not differ between the 2 groups. PAE with 100 μm PVA particles resulted in greater reduction in PSA level, but worse IIEF score than PAE with 200 μm PVA particles; IPSS, QOL score, Qmax, PVR, PV and poor clinical outcome did not differ between the 2 groups. The authors concluded that the evidence on different aspects of PAE was limited. They stated that further studies are needed to examine the role of PAE as compared to other forms of medical and surgical treatment.

Shim and associates (2017) attempted to overcome the limitations of previous systematic reviews to determine the overall safety and efficacy of PAE compared with standard therapy. Meta-analyses were done of randomized, controlled and single group trials. Meta-regression analysis of the moderator effect was performed with single group analysis. The outcomes measured were mean changes in IPSS, QOL, Qmax, PV, PVR and PSA. Adverse events (AEs) were compared as proportional differences between the embolization group and groups receiving other therapies in comparative studies. A total of 16 studies met selection criteria and were included in the meta-analysis; 3 studies were comparative and included a total of 297 subjects, including 149 in the experimental groups and 148 in the control groups. The other 13 studies were non-comparative and included a total of 750 experimental subjects. Pooled overall standardized mean differences (SMD) for embolization in IPSS, Qmax and PV were significantly impaired in the experimental versus control groups. Overall weighted MD (WMD) for all outcomes except PSA were significantly improved from baseline by embolization treatment in non-comparative studies. Sensitivity analysis of study duration showed that all outcome measurements did not differ before versus after 6 months. The authors concluded that although there is growing evidence of the safety and efficacy of PAE for BPH, this systematic review using meta-analysis and meta-regression showed that PAE should still be considered an experimental treatment modality.

Ray et al (2018) examined the safety and efficacy of PAE for lower urinary tract symptoms (LUTS) secondary to BPH and conducted an indirect comparison of PAE with TURP. As a joint initiative between the British Society of Interventional Radiologists, the British Association of Urological Surgeons and the National Institute for Health and Care Excellence, these researchers conducted the UK Register of Prostate Embolization (UK-ROPE) study, which recruited 305 patients across 17 UK urological/interventional radiology centers, 216 of whom underwent PAE and 89 of whom underwent TURP. The primary outcomes were IPSS improvement in the PAE group at 12 months post-procedure, and complication data post-PAE. They also aimed to compare IPSS score improvements between the PAE and TURP groups, using non-inferiority analysis on propensity-score-matched patient pairs. The clinical results and urological measurements were performed at clinical sites; IPSS and other questionnaire-based results were mailed by patients directly to the

trial unit managing the study. All data were uploaded centrally to the UK-ROPE study database. The results showed that PAE was clinically effective, producing a median 10-point IPSS improvement from baseline at 12 months post-procedure. PAE did not appear to be as effective as TURP, which produced a median 15-point IPSS score improvement at 12 months post-procedure. These findings were further supported by the propensity score analysis, in which these investigators formed 65 closely matched pairs of patients who underwent PAE and patients who underwent TURP. In terms of IPSS and QOL improvement, there was no evidence of PAE being non-inferior to TURP. Patients in the PAE group had a statistically significant improvement in Qmax and PV reduction at 12 months post-procedure. PAE had a re-operation rate of 5 % before 12 months and 15 % after 12 months (20 % total rate), and a low complication rate. Of 216 patients, 1 had sepsis, 1 required a blood transfusion, 4 had local arterial dissection and 4had a groin hematoma; 2 patients had non-target embolization that presented as self-limiting penile ulcers. Additional patient-reported outcomes, pain levels and return to normal activities were very encouraging for PAE; 74 % of PAE cases were performed as out-patient or day cases. In contrast, 80 % of TURP cases required at least 1 night of hospital stay, and the majority required 2 nights. The authors concluded that these findings indicated that PAE provided a clinically and statistically significant improvement in symptoms and QOL, although some of these improvements were greater in the TURP arm. The safety profile and quicker return to normal activities may be seen as highly beneficial by patients considering PAE as an alternative treatment to TURP, with the concomitant advantages of reduced length of hospital stay and need for admission after PAE. These investigators noted that PAE is an advanced embolization technique demanding a high level of expertise, and should be performed by experienced interventional radiologists who have been trained and proctored appropriately. The use of cone-beam computed tomography is encouraged to improve operator confidence and minimize non-target embolizations. The place of PAE in the care pathway is between that of drugs and surgery, allowing the clinician to tailor treatment to individual patients' symptoms, requirements and anatomical variation.

Napal Lecumberri and co-workers (2018) noted that BPH is a prevalent disease associated with lower urinary tract symptoms (LUTS). The standard of care for moderate-to-severe LUTS unresponsive to

pharmacological treatment is TURP. However, this intervention is not exempt from complications; PAE has been described as a new, effective and safe procedure for the treatment of LUTS secondary to BPH. To date, only 1 clinical trial has been published on the use of PAE for LUTS, but the study was methodologically flawed in terms of safety monitoring. Thus, well-designed clinical studies are needed to compare the safety and efficacy of both techniques in the treatment of LUTS secondary to BPH. In a prospective, randomized, non-inferiority clinical trial comparing the safety and efficacy of PAE and TURP in the treatment of BPH-related LUTS, a total of 60 patients diagnosed with BPH with obstructive moderate or severe LUTS refractory to medical therapy and candidates for TURP were randomized to either PAE or TURP. The presence and severity of LUTS were assessed using the validated Spanish version of the IPSS. Primary end-points included improvement in Qmax as measured at baseline and 1 year after the intervention. Improvement in IPSS as measured at baseline and after the intervention, reduction in PV, no deterioration or improvement of sexual function (IIEF), reduction in PSA and PVR, satisfaction of the patient with the operation and AEs occurring during the study were secondary outcome measures. The authors concluded that the objective of this clinical study was to examine if PAE is a valid therapeutic option for LUTS that is not inferior to TURP in terms of safety and efficacy. This study also helped to define the profile of candidates for PAE and analyzed the benefits and complications associated with this new technique.

The authors stated that this study had several drawbacks such as its single-center design, the small patient sample (n = 30 for each group) and the medium-term follow-up period (12 months). In addition, prostate size was measured by ultrasound rather than by prostate magnetic resonance (MR) imaging; this study was limited to patients aged greater than 60 years, and the inclusion of patients was not based on prostate size but on the urologist's selection of candidates to be randomized to TURP or PAE.

In a randomized, open-label, non-inferiority trial, Abt and colleagues (2018) compared PAE with TURP in the treatment of LUTS secondary to BPH in terms of patient reported and functional outcomes. A total of 103 patients aged greater than or equal to 40 years with refractory LUTS secondary to BPH were randomized between February 11, 2014 and May

24, 2017; 48 and 51 patients reached the primary end-point 12 weeks after PAE and TURP, respectively. PAE performed with 250 to 400 µm microspheres under local anesthesia versus monopolar TURP performed under spinal or general anesthesia. Primary outcome was change in IPSS from baseline to 12 weeks after surgery; a difference of less than 3 points between treatments was defined as non-inferiority for PAE and tested with a 1-sided t-test. Secondary outcomes included further questionnaires, functional measures, MRI findings, and AEs; changes from baseline to 12 weeks were compared between treatments with 2-sided tests for superiority. Mean reduction in IPSS from baseline to 12 weeks was -9.23 points after PAE and -10.77 points after TURP. Although the difference was less than 3 points (1.54 points in favor of TURP (95 % CI: -1.45 to 4.52)), non-inferiority of PAE could not be shown ($p = 0.17$). None of the patient reported secondary outcomes differed significantly between treatments when tested for superiority; IPSS also did not differ significantly ($p = 0.31$). At 12 weeks, PAE was less effective than TURP regarding changes in Qmax (5.19 versus 15.34 ml/s; difference of 10.15 (95 % CI: -14.67 to -5.63); $p < 0.001$), PVR (-86.36 versus -199.98 ml; 113.62 (39.25 to 187.98); $p = 0.003$), PV (-12.17 versus -30.27 ml; 18.11 (10.11 to 26.10); $p < 0.001$), and de-obstructive effectiveness according to pressure flow studies (56 % versus 93 % shift towards less obstructive category; $p = 0.003$). Fewer AEs occurred after PAE than after TURP (36 versus 70 events; $p = 0.003$). The authors concluded that the improvement in LUTS secondary to BPH observed 12 weeks after PAE was close to that after TURP. These investigators noted that PAE was associated with fewer complications than TURP but has disadvantages regarding functional outcomes, which should be considered when selecting patients. They stated that further comparative study findings, including longer follow-up, should be evaluated before PAE can be considered as a routine treatment.

In a retrospective study, Bhatia and associates (2018a) examined the safety and efficacy of PAE for the treatment of BPH for prostates greater than or equal to 80 ml. This trial included 93 patients with PVs of greater than or equal to 80 ml treated with PAE from April 2014 through October 2017. Mean patient age was 68.5 years (range of 52 to 88) and mean age-adjusted Charlson co-morbidity index was 3.2 (range of 1 to 8). Exclusion criteria included history of biopsy-proven prostate cancer or catheter dependency. Clinical and urodynamic outcomes were reviewed

at 1, 3, 6, and 12 months. Adverse events were graded according to the Clavien-Dindo classification. Mean PV decreased significantly from 141.7 ml to 98.1 ml at 3 months ($p < 0.01$) and 82.2 ml at 12 months ($p < 0.01$). Significant improvements were seen in 3- and 12-month mean IPSS (22.3 versus 7.1 and 7.3, respectively; $p < 0.01$ for both), QOL (4.4 versus 1.2 and 1.3; $p < 0.01$ for both), and post-void residual volume (196.7 ml versus 92.1 and 61.2 ml; $p < 0.01$ and $p < 0.01$, respectively). Significant improvement was also seen in 3-month mean Qmax: 7.7 ml/s versus 12.8 ml/s ($p < 0.01$); 1 grade II complication of stroke occurred; all other complications were self-limited and grade I. The authors concluded that PAE achieved a clinically and statistically significant improvement in symptom burden and secondary outcome measures in patients with PVs greater than or equal to 80 ml. They stated that PAE may be an alternate treatment for patients for whom conventional surgical options are limited or associated with significant morbidity.

In a retrospective, single-center review, Bhatia et al (2018b) examined the safety and efficacy of PAE in urinary catheter-dependent patients with large PVs and high co-morbidity scores. This review included 30 patients with urinary retention at time of PAE from November 2014 through February 2017. Mean (range) age was 73.1 years (48 to 94), age-adjusted Charlson co-morbidity index was 4.5 (0 to 10), duration of urinary retention was 63.4 days (2 to 224), IPSS-QOL was 5.3 (3 to 6), and PV was 167.3 cm3 (55 to 557 cm3). These parameters were collected at 3, 6, and 12 months after PAE. Trials of voiding were performed approximately 2 weeks after PAE and, if failed, every 2 weeks thereafter; AEs were graded using the Clavien-Dindo classification. At a mean (range) of 18.2 days (1 to 72), 26 (86.7 %) patients were no longer reliant on catheters. Follow-up was obtained in all patients eligible at 3 and 6 months and 17 of 20 (85.0 %) patients eligible at 1 year. Mean (range) IPSS-QOL improved significantly to 1.2 (0 to 5), 0.7 (0 to 4), and 0.6 (0 to 4) at 3, 6, and 12 months (all $p < 0.001$). Mean (range) PV decreased significantly to 115.9 cm3 (27 to 248 cm3) at 3 months ($p < 0.001$); 2 patients experienced grade-II urosepsis complications, which were successfully treated with intravenous antibiotics. All other complications were self-limited grade-I complications. The authors concluded that PAE represented a safe and effective option for management of patients with urinary retention, especially patients with large prostates who were not ideal surgical candidates. Moreover, these

researchers stated further prospective studies are needed to establish the addition of PAE to the urologists armamentarium, especially in patients with urinary retention, large prostate, and significant co-morbid conditions.

In a systematic review and meta-analysis, Malling and colleagues (2019) evaluated the safety and efficacy of PAE in the treatment of BPH with LUTS. A systematic review performed according to the PRISMA guidelines with a pre-specified search strategy for PubMed, Web of Science, Cochrane Library and Embase databases protocol (PROSPERO ID: CRD42017059196). Trials studying the efficacy of PAE to treat LUTS with more than 10 participants and follow-up longer than 6 months were included by 2 independent authors. Outcomes investigated were IPSS, QOL, IIEF-5, PV, PSA, Qmax, PVR and complications. To summarize mean change from baseline, a meta-analysis was done using the random-effects model. The search returned 210 references, of which 13 studies met the inclusion criteria, representing 1,254 patients. Patients in the included studies with data available for meta-analysis had moderate-to-severe LUTS and a mean IPSS of 23.5. Statistically significant ($p < 0.05$) improvements of all investigated outcomes were observed at 12-month follow-up. Major complications were reported in 0.3 % of the cases. The authors concluded that these findings suggested that PAE could reduce moderate-to-severe LUTS in men with BPH with a low risk of complications.

Furthermore, an UpToDate review on "Transurethral procedures for treating benign prostatic hyperplasia" (Cunningham and Kadmon, 2018) states that "Given available evidence, PAE cannot be recommended for most patients with LUTSs due to BPH but may be a viable option for poor surgical candidates, those who are concerned with potential complications (e.g., sexual dysfunction or incontinence) of standard treatments, and those with prostates too large for transurethral procedures (e.g., > 80 to 100 ml). PAE has been endorsed by the Society of Interventional Radiology for the treatment of BPH and the National Institute for Health and Care Excellence (NICE) in the United Kingdom, but is only recommended for use in the context of research by the National Institute for Health and has not been approved by the American Urological Association (AUA)". Prostatic arterial embolization is not listed in the "Summary and Recommendations" of this review.

Zumstein et al (2019) noted that PAE has been introduced into clinical practice for the treatment of LUTS secondary to BPH (BPH-LUTS) despite a lack of high-level evidence. These researchers carried out a systematic review and meta-analysis of clinical trials comparing safety and efficacy of PAE versus established surgical therapies. Medline, Embase, and York CRD were searched up to June 23, 2018. Only comparative studies were included. The risk of bias was assessed by the Cochrane Collaboration tool. Meta-analyses were performed using RevMan 5.3. A total of 5 studies including 708 patients met the selection criteria. Risk of bias was rated high for most of the studies. Mean reduction in the IPSS was lower after PAE compared with standard surgical therapies (MD of 3.80 points [95 % CI: 2.77 to 4.83]; $p < 0.001$). PAE was less efficient regarding improvements in all functional parameters assessed including Qmax, PVR, and reduction of PV. In contrast, patient-reported erectile function (IIEF 5) was better after PAE and significantly fewer AEs occurred after PAE. The authors concluded that moderately strong evidence confirmed the safety and efficacy of PAE in the treatment of BPH-LUTS in the short-term. Significant advantages regarding safety and sexual function, but clear disadvantages regarding all other patient-reported and functional outcomes were found for PAE. These researchers stated that large-scale RCTs including longer follow-up periods are needed before PAE can be considered as a standard therapy and to define the ideal indication for PAE in the management of BPH-LUTS.

Based on the Society of Interventional Radiology (SIR)'s research, a multi-society consensus position statement on PAE for the treatment of lower urinary tract symptoms (LUTS) attributed to BPH (McWilliams et at, 2019) provided the following recommendations:

I. 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)
II. PAE can be considered as a treatment option in patients with BPH and moderate to severe LUTS who have very large prostate glands (greater than 80 cm3), without an upper limit of prostate size. (Level of Evidence: C; strength of recommendation: moderate)
III. 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)

IV. 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)

V. 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)

VI. 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 co-morbidities, coagulopathy, or inability to stop anti-coagulation or anti-platelet therapy. (Level of Evidence: E; strength of recommendation: moderate)

VII. 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)

VIII. 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.)

However, none of the recommendations attained a “A” Level of Evidence.

Insausti et al (2020) compared clinical and functional outcomes of PAE with those of TURP for the treatment of BPH-LUTS. Non-inferiority randomized trial was conducted involving men over 60 years of age with BPH-LUTS. From November 2014 to January 2017, a total of 45 patients were randomized to PAE (n = 23) or to TURP (n = 22). PAE was performed with 300- to 500-μm microspheres with the patient under local anesthesia, whereas bipolar TURP was performed with the patients under spinal or general anesthesia. Primary outcomes were changes in Qmax and IPSS from baseline to 12 months; QOL, and PV changes from baseline to 12 month were secondary outcomes; AEs were compared using the Clavien classification. Mean Qmax increased from 6.1 ml/s in the PAE group and from 9.6 ml/s in the TURP patients (p = 0.862 for non-inferiority), and mean IPSS reduction was 21.0 points for PAE and 18.2

points for TURP subjects (p = 0.080) at 12 months. A greater QOL improvement was reported in the PAE group (3.78 points for PAE and 3.09 points for TURP; p = 0.002). Mean PV reduction was 20.5 cm^3 (34.2 %) for PAE subjects and 44.7 cm^3 (71.2 %) for TURP subjects (p < 0.001). There were fewer AEs reported in the PAE group than in the TURP group (n = 15 versus n = 47; p < 0.001). The authors concluded that reduction of LUTS in the PAE group was similar to that in the TURP group at 12 months, with fewer complications secondary to PAE. Moreover, these researchers stated that long-term follow-up is needed to compare the durability of the symptomatic improvement from each procedure.

The Society of Interventional Radiology (SIR)'s research reporting standards for PAE (Uflacker et al, 2020) concluded that "Although sufficient evidence on PAE does exist and has allowed SIR to publish a multi-society consensus position statement, further high-quality studies (with a focus on non-inferiority) would improve the evidence base in support of this procedure. Adherence to reporting standards for PAE research would decrease the number of publications not providing estimates of variability, such as standard deviation or standard error, which would allow meta-analysis, without imputing data. Meta-analyses are also limited by the longitudinal drop-off of patient populations during studies. Therefore, heterogeneous patient populations are being compared at each study time point. To improve systematic reviews or meta-analyses, investigators are encouraged to share individual-level data by direct collaborations or through public data repositories. As with any developing area of clinical research, the evolution from feasibility to larger-scale studies requires comparisons to established therapies with increasing rigor and prospective study. As PAE indications expand to oncologic applications, other criteria such as oncologic endpoints would merit reporting. These reporting standards are provided as a guide to encourage greater consistency and systematization of future PAE research".

Furthermore, an UpToDate review on "Surgical treatment of benign prostatic hyperplasia (BPH)" (McVary, 2020) states that "Prostatic arterial embolization (PAE) is an experimental minimally invasive surgical treatment (MIST) for BPH. Given the heterogeneity in the available literature and safety concerns regarding radiation exposure,

postembolization syndrome, vascular access, technical feasibility, and adverse events, the 2019 American Urological Association (AUA) BPH clinical guidelines state that currently PAE should only be performed in the context of an experimental clinical trial".

Knight et al (2021) reported a comparative systematic review and meta-analysis of PAE and transurethral resection of the prostate (TURP) for the management of BPH. These researchers carried out a multi-database search for relevant literature on July 15, 2020 to include studies published on or before that date. Search terms used were: (prostate embolization OR prostatic embolization OR prostate embolization OR prostatic embolization) AND (prostatic hyperplasia OR prostatic obstruction). Risk of bias was assessed using Cochrane Collaboration and ROBINS-I criteria. Random-effects meta-analysis was performed using RevMan 5.3. A total of 6 studies with 598 patients were included. TURP was associated with significantly more improvement in maximum urinary flow rate (Qmax) (mean difference = 5.02 mL/s; 95 % confidence interval [CI]: 2.66 to 7.38; $p < 0.0001$; $I2 = 89$ %), prostate volume (mean difference = 15.59 ml; 95 % CI: 7.93 to 23.25; $p < 0.00001$; $I2 = 88$ %), and prostate-specific antigen (PSA) (mean difference = 1.02 ng/ml; 95 % CI: 0.14 to 1.89]; $p = 0.02$; $I2 = 71$ %) compared to PAE. No significant difference between PAE and TURP was observed for changes in International Prostate Symptoms Score (IPSS), IPSS quality of life (IPSS-QoL), International Index of Erectile Function (IIEF-5), and post-void residual (PVR). PAE was associated with fewer adverse events (AEs) (39.0 % versus 77.7 %; $p < 0.00001$) and shorter hospitalization times (mean difference = -1.94 days; $p < 0.00001$), but longer procedural times (mean difference = 51.43 mins; $p = 0.004$). The authors concluded that subjective symptom improvement was equivalent between TURP and PAE. While TURP demonstrated larger improvements for some objective parameters, PAE was associated with fewer AEs and shorter hospitalization times. Level of Evidence = IIa.

The authors stated that the main drawback of this meta-analysis was the relatively small number of studies (n = 6) available comparing PAE and TURP -- especially, because only studies that examined both PAE and TURP in the same analysis could be included. Therefore, review articles that only examined one procedure or the other were not included in the present analysis. The present study also excluded Russo and

colleagues' analysis (2015) -- included in other meta-analyses comparing PAE to surgical intervention for BPH -- given that the authors compared PAE to open prostatectomy (OP), whereas the present review exclusively compared PAE and TURP. Among the RCTs, study by Abt et al (2018) was limited in follow-up time. Nevertheless, as noted by Zumstein et al (2018) outcomes have been shown to remain stable or even improve slightly between 3- and 12-month post-procedure in both PAE and TURP groups. The study by Insausti et al (2020) was also deemed low risk along some criteria, but risk of bias was deemed unclear for several categories given relatively limited available information about study design. The remaining 2 RCTs exhibited high risk of bias along several Cochrane Collaboration criteria, and unclear risk of bias due to patient selection and incomplete data. All 4 studies exhibited unclear or high risk of bias due to lack of blinding of both participants/personnel and outcome assessment.

Furthermore, an UpToDate review on "Surgical treatments of benign prostatic hyperplasia" (McVary, 2021) lists prostatic arterial embolization as one of the "Experimental and Emerging Technologies". It states that "Prostatic arteries may be very difficult to identify because of a lack of pathognomonic findings. Nontargeted embolization may lead to ischemic complications of the prostate, bladder, or seminal vesicles. Other short-term complications, including urethral burning sensation, nausea, and vomiting, which have been called the "post-PAE syndrome," are common. Furthermore, radiation and contrast toxicity may lead to additional adverse events".

Acupuncture for the Treatment of Benign Prostatic Hypertrophy

In a systematic review and meta-analysis, Zhang and colleagues (2017) evaluated the therapeutic and adverse effects of acupuncture for BPH in RCTs. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Medline, Embase, the Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and the Wanfang Database. Parallel-group RCTs of acupuncture for men with symptomatic BPH were included. Data from the included trials were extracted by 2 independent reviewers and were analyzed with the Cochrane Collaboration Review Manager software (RevMan 5.3.5) after risk of bias judgments. The

primary outcome measure of this review was a change in urological symptoms. A total of 8 RCTs, which involved 661 men with BPH, were included. Follow-up varied from 4 weeks to 18 months. Pooling of the data from 3 trials that compared acupuncture with sham-acupuncture revealed that in the short term (4 to 6 weeks), acupuncture can significantly improve IPSS (MD -1.90, 95 % CI -3.58 to -0.21). A sensitivity analysis of the short-term endpoint showed the same result (mean difference [MD] -3.01, 95 % CI: -5.19 to -0.84) with a borderline minimal clinical important difference (MCID). Qmax of the short-term endpoint indicated statistically positive beneficial effects of acupuncture (MD -1.78, 95 % CI: -3.43 to -0.14). A meta-analysis after medium-term follow-up (12 to 18 weeks) indicated no significant effect on IPSS when the data from 2 trials were combined (MD -2.04, 95 % CI: -4.19 to 0.10). The authors concluded statistically significant changes were observed in favor of acupuncture in moderate-to-severe BPH with respect to short-term follow-up end-points. They stated that the clinical significance of these changes needs to be tested by further studies with rigorous designs and longer follow-up times.

MRI-Guided Laser Focal Ablation for the Treatment of Benign Prostatic Hypertrophy

Zhang et al (2016) stated that all available surgical treatments for benign prostatic hyperplasia (BPH) have their individual advantages or disadvantages. However, the lack of head-to-head studies comparing different surgeries makes it unavailable to conduct direct analysis. To compare the safety and effectiveness among different lasers and transurethral resection of prostate (TURP) for BPH, randomized controlled trials (RCTs) were searched in Medline, Embase, Cochrane library, WHO International Clinical Trial Registration Platform, and ClinicalTrial.gov by May 2015; and the effectiveness-, peri-operation- and complication-related outcomes were assessed by network meta-analysis. A total of 36 studies involving 3,831 patients were included. Holmium laser through resection and enucleation had the best efficacy in maximum flow rate. Thulium laser through vapo-resection was superior in improving international prostate symptom score and holmium laser through enucleation was the best for post-voiding residual volume improvement. Diode laser through vaporization was the rapidest in removing post-operative indwelling catheter, while TURP was the

longest. TURP required the longest hospitalization and thulium laser through vapo-resection was relatively shorter. Holmium and thulium lasers appeared to be relatively better in surgical safety and effectiveness, so that these 2 lasers might be preferred in selection of optimal laser surgery. The authors concluded that more large-scale and high quality head-to-head RCTs are needed to validate the conclusions. This review did not mention MRI-guided laser focal ablation as a therapeutic option for BPH.

Furthermore, an UpToDate review on "Transurethral procedures for treating benign prostatic hyperplasia" (Cunningham and Kadmon, 2017) does not mention MRI-guided laser focal ablation as a therapeutic option.

Measurement of Blood-based microRNAs for Differential Diagnosis of Prostate Cancer and BPH

Al-Kafaji and co-workers (2018) stated that prostate cancer (PCa) is the second most diagnosed malignancy, and the leading cause of cancer-associated mortality among men; and PSA has long been used for the detection of PCa. However, PSA levels increase in PCa and BPH, and are associated with a poor disease outcome. Circulating microRNAs (miRNAs) have been determined to be highly stable in the circulation, and could be utilized as biomarkers to improve disease diagnosis and management. In the present study, the effectiveness of 4 PCa-associated miRNAs in the discrimination of PCa from BPH and the risk-stratification of PCa was assessed. The study included 100 participants: 35 patients with localized PCa, 35 patients with BPH and 30 healthy subjects. Patients with PCa were categorized based on their tumor stage (T), PSA level and Gleason score (GS) into low-(T 1/2, PSA less than 10 ng/ml or GS less than or equal to 7) and high-risk groups (T 3/4, PSA greater than 20 ng/ml or GS greater than or equal to 8). Reverse transcription-quantitative polymerase chain reaction (RT-PCR) was employed to assess the miRNA expression in peripheral blood samples. Significantly reduced expression of miR-15a, miR-126, miR-192 and miR-377 was observed in patients with PCa compared with patients with BPH and healthy subjects. In addition, the expression of the 4 miRNAs was lower in high-risk PCa patients than in low-risk PCa patients, with miR-126 being the most down-regulated. The expression of the 4 miRNAs was also significantly and independently associated with PCa. Receiver

operating characteristic curve analysis revealed a significant ability of the miRNAs to distinguish patients with PCa from those with BPH, patients with PCa from controls and low-risk PCa from high-risk PCa. The authors concluded that these data suggested that expression of these miRNAs in the blood circulation may be promising, non-invasive biomarkers for the early detection of localized PCa, and for PCa risk stratification. They stated that further validations of the clinical implementation of these results are needed in a larger cohort.

The authors concluded that the small sample size in the present study may limit the statistical power of the results, and further validation studies for the clinical implementation of the results are needed with a larger sample size. Furthermore, the present study focused solely on the potential of miR-15a, miR-126, miR-192 and miR-377 as biomarkers for the early detection of localized PCa or PCa risk stratification. These researchers stated that additional studies are underway in the authors' laboratory to examine the clinical significance of other PCa-associated miRNA biomarkers.

Greco and associates (2019) evaluated the evidence implicating miRNAs in the pathogenesis of BPH. A systematic search of the PubMed and Embase databases was performed using the terms "benign prostate hypertrophy and miRNA" or ("benign prostate hypertrophy and microRNAs" or "miRNA" or "miR") on July 31, 2017. A total of 64 miRNAs from 37 selected articles were ranked according to p values ($p \leq 0.05$). To avoid false positive results, Benjamini-Hochberg correction of p values was performed. Application of the robust rank aggregation method identified miR-221 as significantly associated with BPH ($p = 0.013$). The effect size (ES) was calculated for studies with miR-221 data to generate an estimate of the overall ES and its CI. The ES for miR-221 was measured by the SMD obtained by dividing the difference in the average gene expression between the PCa and BPH groups by a pooled estimate of SD. The random effects model was used to calculate the pooled ES due to the presence of heterogeneity among studies. Publication bias of the 7 included studies was assessed by the Funnel plot and Egger's test and it was detected in the overall analysis of the 7 studies ($p < 0.01$). After the trim and fill procedure, Egger's test revealed

no evidence of publication bias (p = 0.76). The authors concluded that miR-221 has the potential to be used both as a biomarker and novel target in the early diagnosis and therapy of BPH.

Measurement of Seminal Cell Free DNA Concentration for Differential Diagnosis of Prostate Cancer and BPH

Ponti and colleagues (2018) noted that seminal plasma cfDNA (scfDNA) was recently proposed as a novel PCa biomarker. These researchers examined if scfDNA could differentiate PCa from BPH patients. A cohort of 43 patients (18 and 25 pathology proven PCa and BPH patients), and 13 healthy age-matched control subjects were enrolled; scfDNA quantification was performed. Data were analyzed through ANOVA testing. Average scfDNA concentrations were 1,407.83 ng/µl, 128.13 ng/µl and 78.09 ng/µl for PCa patients, BPH patients and healthy subjects, respectively. Statistical analysis showed a significant difference among the groups, allowing for distinction of patients with optimal accuracy. A cut-off level of 450 ng/µl scfDNA was identified for the differentiation of PCa and BPH patients. The authors concluded that scfDNA concentrations were significantly different between PCa patients and BPH patients. They stated that scfDNA is a promising biomarker with several applications in PCa diagnosis, screening programs and therapeutic monitoring.

Temporary Implantable Nitinol Device for the Treatment of BPH

Porpiglia and colleagues (2018) reported 3-year follow-up results of the first implantations with a temporary implantable nitinol device (TIND ; Medi-Tate Ltd., Or Akiva, Israel) for the treatment of LUTS secondary to BPH. A total of 32 patients with LUTS were enrolled in this prospective study. Inclusion criteria were: age of greater than 50 years, IPSS of greater than or equal to 10, Qmax pf less than 12 ml/s, and prostate volume of less than 60 ml. The TIND was implanted within the bladder neck and the prostatic urethra under light sedation, and removed 5 days later in an out-patient setting. Demographics, peri-operative results, complications (according to Clavien-Dindo classification), functional results, and QOL were evaluated. Follow-up assessments were made at 3 and 6 weeks, and 3, 6, 12, 24 and 36 months after the implantation. The Student's t-test, 1-way analysis of variance (ANOVA) and Kruskal-

Wallis tests were used for statistical analyses. At baseline, the mean (standard deviation, S.D.) patient age was 69.4 (8.2) years, prostate volume was 29.5 (7.4) ml, and Qmax was 7.6 (2.2) mL/s. The median (interquartile range, IQR) IPSS was 19 (14-23) and the QoL score was 3 (3-4). All the implantations were successful, with a mean total operative time of 5.8 min. No intraoperative complications were recorded. The change from baseline in IPSS, QOL score and Qmax was significant at every follow-up time-point. After 36 months of follow-up, a 41 % rise in Qmax was achieved (mean of 10.1 ml/s), the median (IQR) IPSS was 12 (6 to 24) and the IPSS QoL was 2 (1 to 4); 4 early complications (12.5 %) were recorded, including 1 case of urinary retention (3.1 %), 1 case of transient incontinence due to device displacement (3.1 %), and 2 cases of infection (6.2 %). No further complications were recorded during the 36-month follow-up. The authors concluded that extended follow-up period corroborated previous findings and suggested that TIND implantation was safe, effective and well-tolerated, for at least 36 months after treatment.

In a systematic review, Bertolo and associates (2018) provided a narrative synthesis of the available literature regarding the role of the TIND for the treatment of BPH-related LUTS, specifically focusing on the follow-up data. The authors concluded that current available evidences are limited in this topic. Sample size of patients available for analysis is small. Moreover, the duration of follow-up period is intermediate and longer follow-up is needed. At the available 3 years follow-up, the TIND implantation is safe, effective, and well-tolerated. The extended follow-up of the first and only available cohort of patients who underwent TIND for LUTS related to BPH corroborated previous literature findings. These researchers stated that further studies are needed to evaluate the durability of TIND outcomes over a longer follow-up, to better define the indications of this approach, and to demonstrate the advantages of second-generation device over the first.

Marcon and co-workers (2018) noted that there is growing interest in minimally invasive (MI) therapeutic options for male LUTS. Among these options, the TIND is a novel instrument used to alleviate symptoms by creating incisions in the prostate via mechanical stress. These investigators reviewed recent data for TIND as an MI procedure to improve LUTS. Medline, PubMed, the Cochrane Database, and Embase were screened for clinical trials, RCTs, and review articles on the use of

TIND in patients with male LUTS. There are currently 2 studies available, 1 being a follow-up of the first pilot study. Both 12-month and 36-month results suggested at least medium-term effects of TIND in terms of symptom improvement (IPSS and Qmax); IPSS was improved by 41 % after 12 months ($p < 0.001$) and worsened only insignificantly after 36 months compared to baseline values; Qmax increased by 4.4 ml/s after 12 months ($p < 0.001$) and did not decrease significantly after 36 months . Post-operative complications were mild and included urinary tract infection and urinary retention. The authors concluded that preliminary data suggested that TIND is a safe and effective MI technique for patients with male LUTS. These researchers stated that symptom relief and increase in urinary flow after 36 months are promising; however, long-term results are needed.

Magistro and colleagues (2018) stated that the first clinical evaluation of the TIND proved its feasibility, safety, and efficacy for the treatment of LUTS over a 3-year follow-up period. However, prospective RCTs are still needed to evaluate its true benefit. New ablative technologies like Rezūm are based on convective water vapor energy and have shown good results in a sham-controlled RCT for the treatment of LUTS over a follow-up period of 3 years. Of note, this procedure was also successful in patients with a prominent middle lobe, and no impairment of sexual function was reported after Rezūm. Innovative technologies like Aquablation (AquaBeam) are still in their infancy, but the first clinical outcomes are promising, even in comparison with the reference method TURP.

Furthermore, UpToDate reviews on "Lower urinary tract symptoms in men" (McVary abd Saini, 2018) and "Transurethral procedures for treating benign prostatic hyperplasia" (Cunningham and Kadmon, 2018) do not mention temporary implantable nitinol device as a therapeutic option.

Amparore and colleagues (2019) stated that in the past 10 years, there has been a growing interest in minimally invasive treatment for BPH associated with LUTS. In this field, one of the options currently available is the temporary implantable nitinol device (iTIND) (Medi-Tate; Medi-Tate Ltd., Or Akiva, Israel). These investigators reviewed the recent data available in the literature regarding the role of the first-generation (TIND) and second-generation (iTIND) devices for the management of BPH with

LUTS, especially focusing on follow-up of functional outcomes. PubMed, Embase, and the Cochrane Central Register of Controlled Trials were screened for clinical trials on this topic. Literature evidences regarding implantation of TIND and iTIND for PBH with LUTS were limited. There were only 3 studies available, 1 with a medium-term follow-up. The results of these studies suggested that both the TIND and iTIND implantations were safe, effective, and well-tolerated procedures, allowing spare ejaculation in sexually active patients. The authors concluded that current evidences emphasize that the temporary implantable nitinol devices are promising alternatives to the standard minimally invasive surgical options for BPH-related LUTS. These researchers stated that further studies are needed to confirm the effectiveness of iTIND over a long-term follow-up.

Porpiglia and associates (2019) reported the clinical experience with a second-generation of iTIND for the treatment of LUTS due to BPH after 1 year of follow-up. A total of 81 patients with LUTS, IPSS greater than or equal to 10, Qmax less than or equal to 12 ml/s, and prostate volume less than 75 ml, were enrolled in this prospective Research Ethics Committee-approved multi-center study. The main exclusion criteria were: hemostatic disorders, PVR greater than 250 ml, obstructive median lobe, and previous prostate surgery. The iTIND was implanted within the bladder neck and the prostatic urethra under light sedation, using a rigid cystoscope. The device was removed 5 to 7 days later in an out-patient setting. Demographics, peri-operative results, complications (according to the Clavien-Dindo system), functional results and QOL were evaluated. Follow-up assessments were conducted at 1, 3, 6 and 12 months post-operatively. The mean (SD) patient age was 65 (8.9) years, prostate volume was 40.5 (12.25) ml, Qmax was 7.3 (2.6) ml/s, IPSS was 22.5 (5.6), and the median (IQR) IPSS QoL score was 4 (2 to 5). All the implantations were successful, with no intra-operative complications recorded; all patients were discharged on the same day of surgery. The devices were retrieved at a mean (SD) of 5.9 (1.1) days after implantation, typically under topical anesthesia. No Clavien-Dindo Grade greater than II complications were recorded. The mean (SD) Qmax at the 1 month follow-up visit was 11.2 (5.7) ml/s and continued to improve thereafter, reaching 14.7 (8.1) ml/s at the 12-month follow-up visit (+100 %). The mean (SD) IPSS urinary symptom scores were 11.7 (8.0) after 1 month and further improved to 8.8 (6.4) at the 12-month follow-up (-60

%). In parallel, the mean (SD) IPSS QoL score drop reached 1.6 (1.3) by the end of the study. During the 12-month period, 2 patients (2.4 %) required medical therapy for BPH, 2 patients (2.4 %) required TURP, while 10 patients were lost to follow-up (12.3 %). As compared to baseline, none of the 61 sexually active patients who completed the 12-month follow-up period reported sexual or ejaculatory dysfunction. The authors concluded that iTIND implantation was feasible, safe and effective in providing relief of BPH-related symptoms, at least until 12 months post-operatively; sexual and ejaculatory functions were fully preserved. Moreover, these researchers stated that further studies with a longer follow-up period are needed to evaluate the durability of these findings and define the indications for iTIND implantation.

Aquablation / Waterjet Ablation / AquaBeam

In a phase-II clinical trial, Gilling et al (2017) sought to establish the safety and effectiveness of aquablation, a novel, image guided, robotic assisted, water jet tissue ablation technology, for the treatment of benign prostatic hyperplasia (BPH). These researchers performed a prospective, single-arm, multi-center trial at 3 centers in Australia and New Zealand with 1-year follow-up. Participants were men 50 to 80 years old with moderate-to-severe lower urinary tract symptoms (LUTS) as determined by urodynamics. All patients underwent aquablation under image guidance. Primary end-points included procedural and peri-operative safety. The main clinical end-point was the change from baseline in I-PSS (International Prostate Symptom Score). Other secondary end-points included uroflow measures, prostate volume (PV) on transrectal ultrasound (TRUS) and detrusor pressure. Detrusor pressure at maximum flow was only measured at 6 months. A total of 21 men underwent aquablation at a mean age of 69.7 years (range of 62 to 78); PV was 57.2 ml (range of 30 to 102). Procedural duration averaged 38 mins with a mean aquablation treatment time of 5 mins. All but 1 subject were catheterized for 1 day only and 19 of 21 were discharged home the day after the procedure. Detrusor pressure at maximum flow decreased from 65 cm H2O at baseline to 39 cm H2O at 6 months ($p < 0.0027$); PV decreased from 57 ml at baseline to 35 ml ($p < 0.0001$). Mean I-PSS score improved from 23.0 at baseline to 6.8 at 12 months ($p < 0.0001$) and maximum urinary flow increased from 8.7 to 18.3 ml per second ($p < 0.0001$). There were no important peri-operative adverse events (AEs)

No urinary incontinence (UI) developed and sexual function was preserved post-operatively. The authors concluded that the findings of this phase-II trial provided early evidence to support the safety and effectiveness of aquablation for symptomatic BPH. The main limitations of this study were its small sample size (n = 21), short-term follow-up (1 year), and the lack of a concurrent control group; and the editorial comment noted that there are still many questions yet to be resolved regarding this technology and technique.

Desai et al (2018) reported procedure process improvements and confirmed the preserved safety and short-term effectiveness of a second-generation Aquablation device for the treatment of LUTS attributable to BPH in 47 consecutive patients at a single institution. Baseline, peri-operative and 3-month urinary function data were collected. The mean (range) patient age was 66 (50 to 79) years, and TRUS-measured PV was 48 (20 to 118) ml. A median lobe was present in 25 patients (53 %) and 8 patients had catheter-dependent urinary retention. The mean (range) total procedure time was 35 (13 to 128) mins and the tissue resection time was 4 (1 to 10) mins; 5 Clavien-Dindo grade I/II and 5 Clavien-Dindo grade III complications were recorded in 8 patients. The mean (range) hospital stay was 3.1 (1 to 8) days and the mean (range) duration of urethral catheterization was 1.9 (1 to 11) days. The mean I-PSS decreased from 24.4 at baseline to 5 at 3 months; IPSS quality-of-life (QOL) score decreased from 4.5 to 0.3 points; peak urinary flow rate increased from 7.1 to 16.5 ml/s and post-void residual (PVR) urine volume decreased from 119 to 43 ml (all $p < 0.01$). The authors concluded that this study confirmed procedure process improvements resulting from system enhancements, with preservation of safety and effectiveness during use of a second-generation device for the treatment of LUTS attributable to BPH in the largest single-institution study conducted to-date. These researchers stated that comparative studies against established transurethral techniques will probably determine the role of Aquablation in the surgical treatment of symptomatic BPH.

The authors stated that limitations of this study included the following. Throughout the treatment of this cohort, several parameters and treatment settings were improved to derive the best workflow. Whether these improvements affected safety or decreased symptom-reduction efficacy in the long-term was not known. The study did not have long-

term follow-up (many patients were from outlying rural areas and such follow-up was not feasible); however, the focus of the study was the confirmation of device system enhancements as well as feedback on usability from multiple surgeons. Nonetheless, short-term safety and efficacy up to 3 months were consistent with the 3-month results reported in previous studies. Finally, for cultural reasons, the study did not include questions about sexual function, an important topic. Although previous reports have suggested preserved sexual function after Aquablation, prospective trials are underway comparing sexual function results, as well as other safety and effectiveness measures, against TURP outcomes.

Yafi et al (2018) noted that between September and December 2017, a total of 82 men with moderate-to-severe LUTS due to BPH and PV of 80 to 150 cc underwent Aquablation in a prospective, multi-center clinical trial in the United States. Baseline patient and clinical demographics and standardized post-operative parameters were collected and tabulated in a central independently monitored database; AEs through 3 months were adjudicated by an independent clinical events committee. Mean pre-treatment PV was 108 ± 21.1 cc. Mean operative time was 38.2 ± 14.4 mins and mean Aquablation resection time was 7.7 ± 3.3 mins. Additional electrocautery for hemostasis was not needed in any patient following Aquablation. The average length of stay (LOS) following the procedure was 1.6 ± 1.0 days. Mean pre- and 3 months post-treatment I-PSS scores were 23.7 ± 6.4 and 7.1 ± 5.1, -16.6, $p < 0.01$. Mean pre- and 3 months post-treatment Qmax were 9.2 ± 3.3 ml/s and 19.5 ± 13 ml/s, + 10.8 ml/s, $p < 0.01$. Mean pre- and 3 months post-treatment PVRs were 120.6 ± 119.1 cc and 50.6 ± 61.6 cc, -72.0 cc, $p < 0.01$. The observed Clavien-Dindo grade 2 or higher event rate at 3 months was 34.1 %. The authors concluded that Aquablation was a safe and effective therapeutic option for men with large prostates (80 to 150 cc) suffering from LUTS/BPH. Moreover, they stated that longer-term data are needed to validate Aquablation as a durable treatment for LUTS/BPH. The major drawbacks of this study were its short-term follow-up (3 months), relatively small sample size (n = 82); and the lack of a control group.

In a prospective, multi-center, double-blind, randomized controlled trial (RCT), Gilling et al (2018) reported 6 months outcomes comparing the safety and efficacy of Aquablation and trans-urethral resection of the prostate (TURP) for the treatment of LUTs related to BPH. A total of 181

patients with moderate-to-severe LUTS related to BPH underwent TURP or Aquablation. The primary efficacy end-point was the reduction in I-PSS at 6 months. The primary safety end-point was the development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications. Mean total operative time was similar for Aquablation and TURP (33 versus 36 mins, p = 0.2752) but resection time was lower for Aquablation (4 versus 27 mins, p < 0.0001). At 6-month, patients treated with Aquablation and TURP experienced large I-PSS improvements. The pre-specified study non-inferiority hypothesis was satisfied (p < 0.0001). Of the patients who underwent Aquablation and TURP, 26 % and 42 %, respectively, experienced a primary safety end-point, which met the study primary non-inferiority 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 % versus 36 %, p = 0.0003). The authors concluded that surgical prostate resection using Aquablation showed non-inferior symptom relief compared to TURP; but with a lower risk of sexual dysfunction; larger prostates (50 to 80 ml) demonstrated a more pronounced superior safety and efficacy benefit. These researchers stated that these findings suggested that Aquablation of the prostate may be a safe and effective approach for the treatment of LUTS associated with BPB; they stated that longer term follow-up would help evaluate the clinical value of Aquablation.

Hwang et al (2019) stated that new, minimally invasive surgeries have emerged as alternatives to TURP for the management of LUTS in men with BPH. Aquablation is a novel, minimally invasive, water-based therapy, combining image guidance and robotics for the removal of prostatic tissue. In a Cochrane review, these investigators examined the effects of Aquablation for the treatment of LUTS in men with BPH. They performed a comprehensive search using multiple databases (the Cochrane Library, Medline, Embase, Scopus, Web of Science, and LILACS), trials registries, other sources of grey literature, and conference proceedings published up to February 11, 2019, with no restrictions on the language or status of publication. They included parallel-group RCTs and cluster-RCTs, as well as non-randomized observational prospective studies with concurrent comparison groups in which participants with BPH who underwent Aquablation. Two review authors independently assessed studies for inclusion at each stage, and undertook data

extraction and "risk of bias" and GRADE assessments of the certainty of the evidence. They considered review outcomes measured up to and including 12 months after randomization as short-term and beyond 12 months as long-term. These researchers included 1 RCT with 184 subjects comparing Aquablation to TURP. The mean age and I-PSS were 65.9 years and 22.6, respectively. The mean PV was 53.2 ml. They only found short-term data for all outcomes based on a single randomized trial. Primary outcomes up to 12 months, Aquablation likely resulted in a similar improvement in urologic symptom scores to TURP (mean difference (MD) -0.06, 95 % confidence interval (CI): -2.51 to 2.39; participants = 174; moderate-certainty evidence). They down-graded the evidence certainty by one level due to study limitations. Aquablation may also result in similar quality of life (QOL) when compared to TURP (MD 0.27, 95 % CI: -0.24 to 0.78; participants = 174, low-certainty evidence). They down-graded the evidence certainty by two levels due to study limitations and imprecision. Aquablation may result in little to no difference in major AEs (risk ratio (RR) 0.84, 95 % CI: 0.31 to 2.26; participants = 181, very low-certainty evidence); but they were very uncertain of this finding. This would correspond to 15 fewer major AEs per 1,000 participants (95 % CI: 64 fewer to 116 more). They down-graded the evidence certainty by one level for study limitations and two levels for imprecision. Secondary outcomes up to 12 months, Aquablation may result in little to no difference in re-treatments (RR 1.68, 95 % CI: 0.18 to 15.83; participants = 181, very low-certainty evidence); but they were very uncertain of this finding. This would correspond to 10 more re-treatments per 1,000 participants (95 % CI: 13 fewer to 228 more). They down-graded the evidence certainty by one level due to study limitations and two levels for imprecision. Aquablation may result in little to no difference in erectile function as measured by International Index of Erectile Function questionnaire Erectile Function domain compared to TURP (MD 2.31, 95 % CI: -0.63 to 5.25; participants = 64, very low-certainty evidence), and may cause slightly less ejaculatory dysfunction than TURP, as measured by Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MD 2.57, 95 % CI: 0.60 to 4.53; participants = 121, very low-certainty evidence). However, they were very uncertain of both findings. These researchers down-graded the evidence certainty by two levels due to study limitations and one level for imprecision for both outcomes. They 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 authors concluded that based on short-term (up to 12 months) follow-up, the effect of Aquablation on urological symptoms was probably similar to that of TURP (moderate-certainty evidence). The effect on QOL may also be similar (low-certainty evidence). They were very uncertain whether patients undergoing Aquablation were at higher or lower risk for major AEs (very low-certainty evidence). They were 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). These conclusions were based on a single study of men with a PV up to 80 ml in size. These researchers stated that longer-term data and comparisons with other modalities appeared critical to a more thorough assessment of the role of Aquablation for the treatment of LUTS in men with BPH.

In a systematic review, Reale et al (2019) evaluated functional outcomes (Qmax, QOL, I-PSS, PVR), sexual outcome (erectile dysfunction [ED] and anejaculation rate), and AEs evaluated according to the Clavien-Dindo classification. The bibliographic search with the included terms (prostate, benign prostatic hyperplasia, benign prostatic enlargement, lower urinary tract symptoms, water jet dissection, aquablation, AquaBeam) produced a literature of 32 articles altogether. After removing papers of not interest or articles which the outcomes could not be deduced, 9 studies were examined for a total of 664 patients screened. The functional outcomes, evaluated after water jet dissection, have shown improvement with respect to the baseline in all the selected articles. In the comparison papers with the TURP, the Aquablation has been statistically not inferior regarding functional outcomes. The sexual outcomes have highlighted a better ejaculation rate for water jet dissection than TURP. Regarding the AEs, water jet dissection documented low rates of AEs and, in comparison studies, were not statistically superior than TURP. The authors concluded that the AquaBeam System for the treatment of LUTS/BPH has proven to be a safe technique that provided functional outcomes comparable to TURP. About sexual outcomes, the most important data were certainly the low rate of retrograde ejaculation. Moreover, these researchers stated that other multi-center randomized trials with larger cohorts and longer follow-up are still needed.

Misrai et al (2019) noted that Aquablation has emerged as a novel ablative therapy combining image guidance and robotics for targeted waterjet adenoma resection. These researchers described a standardized technique of aquablation in the treatment of benign prostatic obstruction (BPO), and reported the peri-operative and 1-year functional outcomes obtained by multiple surgeons with no previous experience of the technique. Between September 2017 and January 2018, patients referred to 3 different urological centers for BPO surgical management were prospectively enrolled to undergo an aquablation procedure, which was performed using the AquaBeam system (Procept BioRobotics, Redwood Shores, CA) that combines transrectal prostatic image guidance and robotics bespoke tissue resection with a high-pressure saline jet. The surgeon defined the area of treatment, and the resection is executed automatically. The primary end-point was the change in total I-PSS score at 6 and 12 months. Functional outcomes were assessed at 1, 3, 6, and 12 months with I-PSS, International Index of Erectile Function (I-IEF)-15, Sexual Health Inventory for Men, and Male Sexual Health Questionnaire questionnaires and uroflowmetry. A total of 30 patients were enrolled in the study. The median operative time and resection time were 30.5 (24 to 35) and 4 (3.1 to 4.9) mins, respectively. The median catheterization time was 43 (23 to 49) hours. The median hospitalization stay was 2 (2 to 4) days. The I-PSS score improved to 3 (1 to 6) at the 6 months, with a mean change of 15.6 points (95 % CI: 13 to 18.2); I-PSS improvements persisted at month-12. The maximum urinary flow rate improved to 20.4 (17 to 26) ml/s at 12 months. The 6-month rates of Clavien-Dindo grade 2 and 3 events were 13.3 %. There were no reports of incontinence or de-novo ED. Post-operative de-novo ejaculatory dysfunction was observed in 26.7 % of patients. The authors concluded that this clinical registry confirmed that aquablation was feasible, safe, and effective, and provided immediate good functional results and similar outcomes to those of prior studies despite the lack of surgeons' previous experience with the technique. These researchers stated that aquablation is feasible, safe, and reproducible with promising outcomes for treating BPH.

Gilling and associates (2019) compared 2-year safety and efficacy outcomes after Aquablation or TURP for the treatment of LUTS related to BPH. A total of 181 patients with BPH were randomly assigned (2:1 ratio) to either Aquablation or TURP. Patients and follow-up assessors were

blinded to treatment. Assessments included the IPSS, MSHQ, IIEF and uroflow. The focus of analysis was 2-year outcomes. At 2 years, IPSS scores improved by 14.7 points in the Aquablation group and 14.9 points in TURP (p = 0.8304, 95 % CI: - 2.1 to 2.6 points). Two-year improvements in Qmax were large in both groups at 11.2 and 8.6 cc/s for Aquablation and TURP, respectively (p = 0.1880, 95 % CI: - 1.3 to 6.4). Sexual function as assessed by MSHQ was stable in the Aquablation group and decreased slightly in the TURP group. At 2 years, PSA was reduced significantly in both groups by 0.7 and 1.2 points, respectively; the reduction was similar across groups (p = 0.1816). Surgical re-treatment rates after 12 months for Aquablation were 1.7 % and 0 % for TURP. Over 2 years, surgical BPH re-treatment rates were 4.3 % and 1.5 % (p = 0.4219), respectively. The authors concluded that 2-year efficacy outcomes after TURP and Aquablation were similar, and the rate of surgical re-treatment was low and similar to TURP; Aquablation may be an alternative for men who strongly prefer maintenance of ejaculatory function. (ClinicalTrials.gov number, NCT02505919).

Gillig and associates (2020) reported on 3-year outcomes comparing the efficacy and safety after prostate resection with Aquablation therapy or transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms related to benign prostate hyperplasia (BPH). The investigators followed 181 patients assigned to either Aquablation therapy or TURP for 3 years postoperatively. Patients and follow up assessors were blinded to treatment. Assessments included International Prostate Symptom Score (IPSS), Male Sexual Health Questionnaire (MSHQ-EjD), International Index of Erectile Function (IIEF) and uroflow. Over 3 years of treatment, improvements in IPSS scores were statistically similar across groups. Mean 3-year improvements were 14.4 and 13.9 points in the Aquablation and TURP groups, respectively (difference of 0.6 points, 95% CI -3.3-2.2, p = .6848). Similarly, 3-year improvements in Qmax were 11.6 and 8.2 cc/sec (difference of 3.3 [95% CI -0.5-7.1] cc/sec, p = .0848). At 3 years, PSA was reduced significantly in both groups by 0.9 and 1.1 ng/mL, respectively; the reduction was similar across groups (p = .5983). There were no surgical retreatments for BPH beyond 20 months for either Aquablation or TURP. The investigators concluded that three-year BPH symptom reduction and urinary flow rate improvement were similar after TURP and Aquablation therapy. No subjects required surgical retreatment beyond 20 months postoperatively. (ClinicalTrials.gov number, NCT02505919).

Bhojani and colleagues (2019) reported 12-month safety and effectiveness outcomes of the WATERII trial, a prospective, multi-center trial of the Aquablation procedure for the treatment of men with symptomatic BPH and large-volume prostates (i.e., between 80 and 150 cc). A total of 101 men with moderate-to-severe BPH symptoms and prostate volumes of 80 to 150 cc underwent a robotic-assisted Aquablation procedure. Functional and safety outcomes were assessed at 12 months post-operatively. Mean prostate volume was 107 cc (range of 80 to 150). Mean operative time was 37 mins and mean Aquablation resection time was 8 mins. The average length of hospital stay following the procedure was 1.6 days. Mean IPSS improved from 23.2 at baseline to 6.2 at 12 months ($p < 0.0001$). Mean IPSS QOL improved from 4.6 at baseline to 1.3 at 12-month follow-up ($p < 0.0001$). Significant improvements were observed in Qmax (12-month improvement of 12.5 cc/sec) and PVR (drop of 171 cc in those with PVR greater than 100 at baseline). Antegrade ejaculation was maintained in 81 % of sexually active men. No patient underwent a repeat procedure for BPH symptoms. There was a 2 % de-novo incontinence rate at 12 months, and 10 patients did require a transfusion post-operatively while 5 required take back fulgurations. At 12 months, PSA reduced from 7.1 ± 5.9 ng/ml at baseline to 4.4 ± 4.3 ng/ml. The authors concluded that the Aquablation procedure was safe and effective in treating men with large prostates (80 to 150 cc) after 1 year of follow-up, with an acceptable complication rate and without a significant increase in procedure or resection time compared to smaller sized glands. ClinicalTrials.gov number, NCT03123250.

The authors stated that that despite its merits to examine the Aquablation procedure in men with BPH and with significantly larger prostates, the main limitation of the WATERII trial was that it was a single-arm study without a control group preventing direct comparisons with those techniques. Furthermore, standardized reporting of events categorized by Clavien-Dindo (CD) scores was limited in the literature. In addition, surgeon experience with Aquablation is still relatively limited and additional experience will probably improve outcomes. Finally, while the outcomes are promising, longer follow-up are needed to confirm these findings.

Desai et al (2020) reported 2-year safety and effectiveness of the Aquablation procedure for the treatment of men with symptomatic benign prostatic hyperplasia (BPH) and large-volume 80-150 cc prostates. Between September-December 2017, 101 men with moderate-to-severe BPH symptoms and prostate volumes of 80-150 cc underwent an ultrasound-guided robotically executed Aquablation procedure in a prospective multicenter international clinical trial (WATER II). Baseline, procedural and follow up parameters were recorded at baseline and scheduled postoperative visits. Herein we report 2-year safety and efficacy for this cohort. Mean prostate volume was 107 cc (range 80-150 cc). Mean IPSS improved from 23.2 at baseline to 5.8 at 2 years (17-point improvement, $p < .0001$). Mean IPSS quality of life improved from 4.6 at baseline to 1.1 at 2 years ($p < .0001$). Maximum urinary flow increased from 8.7 to 18.2 cc/sec. Two subjects underwent a repeat procedure for BPH symptoms over the 2-year follow up period. By 2 years or study exit, all but 2 of 74 subjects stopped taking alpha blockers. Similarly, all but 4 of 32 subjects stopped taking 5α-reductase inhibitors. The investigators concluded that two-year prospective multicenter follow up demonstrated that the Aquablation procedure is safe and effective in the treatment of men with LUTS due to BPH and prostates 80-150 cc with durable treatment efficacy, acceptable safety profile and a low retreatment rate. ClinicalTrials.gov number, NCT03123250.

Bach et al (2020) evaluated the safety and effectiveness of the Aquablation procedure in the commercial setting in 178 men at five sites. The mean prostate volume was 59 cc. The procedure time averaged 24 min and total anesthesia duration was 50 min. The International Prostate Symptom Score (IPSS) decreased from 21.6 at the baseline to 6.5 at the 12-month follow-up, a 15.3-point improvement ($p < 0.0001$). The maximum urinary flow rate increased from 10 cc/s at the baseline to 20.8 cc/s at month 12 (increase of 11.8 cc, $p < 0.0001$). Ejaculatory function was relatively preserved. Prostate volume assessed with transrectal ultrasound decreased 36% by month three. Five patients (2.7%) underwent a transfusion in the first week after the procedure. The authors concluded that real-world evidence shows that Aquablation is safe and effective for the treatment of BPH.

Guidelines from the AAUA (Foster et al, 2019) stated that "Aquablation may be offered to patients with LUTS attributed to BPH provided prostate volume greater than 30 / less than 80 g, however, patients should be informed that long-term evidence of efficacy and re-treatment rates, remains limited. (Conditional Recommendation; Evidence Level: Grade C)". These were "conditional recommendations" based upon evidence about which the panel has a low level of certainty (evidence level Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data)).

Ng and Barber (2019) noted that prostatic hydroablation (Aquablation) is a new technique that entails high velocity water jets used in non-thermal ablation of the obstructing prostatic tissue robotically delivered by a transurethral cystoscopic hand-piece and guided by real time TRUS imaging. In prostatic hydroablation, the initial part of the surgery involved careful treatment planning tailored to the prostatic anatomy with preservation of important landmarks nearby, then, high velocity waterjet streams were delivered to ablate the obstructing prostatic tissue without use of any heat. Following the ablation and removal of hand-piece, a routine cystoscopic bladder washout was performed and hemostasis achieved with balloon tamponade from a 3-way catheter placed under tension using a custom-designed catheter tensioning device. Initial studies involving a few case series and a phase-II clinical trial demonstrated the safety and effectiveness of Aquablation in treatment of symptomatic BPH. Subsequently, a large, multi-center international prospective randomized blinded clinical trial (WATER) was conducted to examine the efficacy of Aquablation versus TURP. Results from this pivotal trial showed non-inferior symptom relief compared to TURP, but with a lower risk of sexual dysfunction. WATER II study was then conducted to evaluate the safety and feasibility from a prospective, multi-center study of Aquablation in the treatment of symptomatic large-volume BPH. The results from this study showed that Aquablation was feasible and safe in treating men with large prostates (80 to 150 ml). The authors concluded that the current landscape of BPH surgical treatment should be individualized with a shared decision-making process based on prostatic anatomy and clinical parameters combined with patient's preferences to select the ideal therapeutic option for each patient. Aquablation is one

such option that involves a robotically delivered hydroablation technique based on individualized real time US prostatic mapping that could offer safe and effective treatment for symptomatic BPH while minimizing sexual dysfunction. Moreover, these researchers stated that larger trials with longer follow-up data are needed to further validate the long term effectiveness of Aquablation.

Roehrborn and associates (2019) noted that invasive procedures, such as TURP, have long been the gold standard therapy for the treatment of LUTS secondary to BPH. Recently, newer treatment modalities have arisen, such as Aquablation, with similar efficacy and improved AE profiles, with particular emphasis on post-operative sexual function. Aquablation is a new technology that utilizes machine-controlled water jets to ablate the soft tissue of the prostate as determined by the doctor. These investigators discussed the techniques currently being used to complete this procedure, the outcomes and safety, and finally, the long-term data as well as the AEs associated with Aquablation. In head-to-head comparison with TURP, Aquablation has equivalent objective results with much shorter resections times, and significantly less sexual side effects. Currently, the literature only reported results extending to 12 months post-procedure, and thus long-term durability of results beyond this time-point remains unknown. The authors concluded that Aquablation is a safe and effective option for treating LUTS secondary to BPH. It is a new surgical option that showed very promising short-term results, in particular, due to its short resection time regardless of gland size and low rate of sexual side effects. This technology still needs further investigation to confirm durability and efficacy over time.

NICE Guidance on "Transurethral water jet ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia" (2019) stated that while the evidence on transurethral water jet ablation for LUTS caused by benign BPH raises no major safety concerns, the evidence on efficacy is limited in quantity; thus, this procedure should only be used with special arrangements. Moreover, NICE encouraged further research into transurethral water jet ablation for LUTS caused by BPH and may update the guidance on publication of further evidence. Further research should report long-term follow-up and include re-intervention rates.

Nguyen et al (2020) compared the outcomes of Aquablation in 30 to 80 ml prostates with those in 80 to 150 ml prostates. Surgical options, especially with short learning curves, are limited when treating large prostates for LUTS due to BPH. Aquablation could solve this issue with global reproducibility, independent of prostate volume. Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue (WATER [W-I]) was a prospective, double-blind, multi-center, international clinical trial comparing Aquablation and TURP for the treatment of LUTS/BPH in prostates between 30 and 80 ml. WATER II (W-II) was a prospective, multi-center, single-arm international clinical trial of Aquablation in prostates between 80 and 150 ml. These researchers compared baseline parameters and 12-month outcomes in 116 W-I and 101 W-II study patients. Students' t-test or Wilcoxon tests were used for continuous variables and Fisher's test for binary variables. The mean (SD) operative time was 33 (17) and 37 (13) mins in W-I and W-II, respectively. Actual treatment time was 4 and 8 mins in W-I and W-II, respectively. The mean change in the IPSS was substantial averaging (at 12 months) 15.1 in W-I and 17.1 in W-II (p = 0.605). By 3 months, Clavien-Dindo grade greater than or equal to II events occurred in 19.8 % of W-I patients and 34.7 % of W-II patients (p = 0.468). The authors concluded that Aquablation clinically normalized outcomes between patients with 30 to 80 ml prostates and patients with 80 to 150 ml prostates treated for LUTS/BPH, with an expected increase in the risk of complications in larger prostates. This study had several drawbacks. These researchers did not directly compare Aquablation to volume-independent surgical alternatives, such as HoLEP and PVP. Doing so would have been particularly beneficial in comparing complications as standardized reporting of events categorized by Clavien-Dindo grades is limited in the literature. With only a 24-month follow-up for W-I and 12-month follow-up for W-II, longer-term follow-up data from these cohorts are needed to demonstrate the durability of the treatment outcomes.

Furthermore, an UpToDate review on "Surgical treatment of benign prostatic hyperplasia (BPH)" (McVary, 2020) states that "Robot-assisted waterjet ablation of the prostate is an emerging technique that uses an image-guided, robotically controlled waterjet, termed AquaBeam, to ablate prostatic tissue (Aquablation). The waterjet serves as a high-velocity hydrodissection tool that ablates prostatic parenchyma while sparing major blood vessels and the prostatic capsule. Transrectal

ultrasound is used to map the prostate prior to the procedure. Aquablation is not a minimally invasive surgical treatment (MIST) procedure, because it requires general anesthesia. Despite significant setup time and effort, it can be performed efficiently. Aquablation may be used to treat LUTS/BPH in patients with a prostate volume between 30 and 80 g. The presence of a large middle lobe and the requirement for general anesthesia are limitations to the technology in some trials".

In a retrospective analysis, Kasraeian et al (2020) characterized procedure variables and outcome data from men undergoing the Aquablation Therapy of the prostate procedure for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). These researchers examined the safety and efficacy of robotically guided waterjet-based prostate resection in the 1st study of all-comers in a single-center, commercial setting in the United States. A total of 55 men underwent the Aquablation of the prostate between July 2018 and December 2019. Mean prostate volume (PV) was 100 cc, and 85 % had a prominent, obstructing middle lobe. Operative time averaged 59 mins, and the mean hemoglobin (Hb) drop was 1 g/dL. A substantial improvement of 80 % (17 points) was observed in BPH symptoms scores. By uroflowmetry, Qmax improved by 182 % (14 ml/sec). Men with PV of greater than 100 cc had similar hospital length of stay (LOS), BPH symptom reduction, and Qmax improvement compared to those with volume of less than 100 cc. The authors concluded that in the setting of a community private urology practice, Aquablation Therapy was safe and effective for the treatment of men with BPH regardless of prostate shape or prostate size. This was a single-center study with 55 subjects with short-term follow-up (3 months); its findings need to be validated by well-designed studies.

In a review on “Current treatment for BPH”, Miernik and Gratzke (2020) stated that Aquablation (waterjet ablation [AquaBeam]) is based on robot-assisted hydro-dissection of the prostate tissue that spares collagenous structures (blood vessels, capsule). Under transrectal ultrasound guidance, the adenoma tissue is removed within limits defined by the surgeon and without generating thermal energy. However, transurethral hemostasis may be required after ablation. Functional outcome at 2 years was comparable to that after TURP, with a lower risk of ejaculatory dysfunction – in a direct comparison, the WATER study showed at 24

months follow-up an anejaculation rate of 10 % for Aquablation versus 36 % for TURP (p = 0.0003). The procedure is efficient for volumes of 30 to 80 ml; however, long-term follow-up data are still awaited. Peri- and post-operative safety aspects of treatment of adenoma volumes greater than 80 ml also need to be examined in further studies. The authors concluded that the safety and efficacy of many new developments in the area of pharmacological and minimally invasive treatment remain to be demonstrated in randomized trials.

In a meta-analysis, Elterman et al (2021a) examined functional outcomes following Aquablation in various PV and anatomical subgroups. This analysis entailed individual patient data undergoing Aquablation therapy from 4 prospective, global, clinical studies that have been carried out with Aquablation; WATER, WATER II, FRANCAIS WATER and OPEN WATER. Subjects included 425 men with LUTS due to BPH with 1-year follow-up. Main outcome measures focused on International Prostate Symptom Score (IPSS), uroflowmetry, post-operative Incontinence Severity Index (ISI) and surgical re-treatment. A total of 425 men with prostates ranging in size from 20 to 150 ml underwent Aquablation therapy. The outcomes from the 7 questions in the IPSS questionnaire were grouped by the following – prostates of less than 100 ml, prostates of greater than or equal to 100 ml, prostate anatomy with an obstructive median lobe identified by imaging, and prostate anatomy without an obstructive median lobe. Regardless of subgroup, all outcomes were consistent and demonstrated a significant improvement from baseline. Specifically, improvements in frequency, urgency and nocturia demonstrated bladder function improvement. Patients entering treatment with severe incontinence, ISI score of greater than 4, and regardless of prostate size, showed a reduction in incontinence during patient follow-up. Surgical re-treatment due to BPH symptoms occurred in 0.7 % (95 % confidence interval [CI]: 0.1 % to 2.0 %). The authors concluded that across a variety of prostate anatomies, Aquablation therapy showed remarkable functional improvements following the index procedure. Furthermore, men with moderate-to-severe LUTS/BPH and over-active bladder (OAB) resulting in urge incontinence showed a reduction in incontinence symptoms post-procedure.

The authors stated that the drawbacks of this meta-analysis included: Data after 1 year were not available in all studies, limiting the potential to examine longer-term outcomes. However, 3-year outcomes after Aquablation appeared to be sustained from the published WATER trial data. The enrolled patient populations and settings were slightly different: WATER (international) and FRANCAIS (France only) enrolled men with smaller prostates (30 to 80 ml); WATER II (North America) enrolled men with larger prostates only (80 to 150 ml); WATER and WATER II were conducted in a pre-market setting whereas FRANCAIS and OPEN WATER were conducted in the post-market setting. The technique using the loop for hemostasis following Aquablation has evolved since the conduct of these trials. Although a thorough review and process was completed to conduct this systematic review, the research was not governed by a registered protocol.

Elterman et al (2021b) examined if focal bladder neck cautery is effective in reducing bleeding following prostate tissue resection for BPH using Aquablation. Consecutive patients at 11 countries in Asia, Europe and North America who underwent Aquablation for symptomatic BPH between late 2019 and January 2021 were included in the analysis. All patients received post-Aquablation non-resective focal cautery at the bladder neck. A total of 2,089 consecutive Aquablation procedures were included. Mean PV was 87 cc (range of 20 cc to 363 cc). Post-operative bleeding requiring transfusion occurred in 17 cases (0.8 %, 95 % CI: 0.5 % to 1.3 %) and take-back to the operating room (OR) for fulguration occurred in 12 cases (0.6 %, 95 % CI: 0.3 % to 1.0 %). This result compared favorably ($p < .0001$) to the previously published hemostasis transfusion rate of 3.9 % (31/801) using methods performed in the years 2014 to 2019. The authors concluded that in PVs averaging 87 cc (range of 20 cc to 363 cc), Aquablation procedures performed with focal bladder neck cautery that required a transfusion post-operatively occurred in a remarkably low number of cases. This study did not provide any data on Aquablation for the treatment of BPH; it presented findings regarding the use of focal bladder neck cautery in the management of post-operative bleeding following Aquablation therapy.

ECRI's Clinical Evidence Assessment on "AquaBeam Robotic System for treating benign prostatic hyperplasia" (2021) noted that the evidence is somewhat favorable. It concluded that "AquaBeam is safe and reduces

BPH-related LUTS for up to 3 years, based on evidence from 2 systematic reviews (SRs), an additional retrospective, non-randomized study, and 4 pre-/post-treatment studies. However, the SRs included only 1 randomized controlled trial (RCT) that compared AquaBeam with transurethral resection of the prostate (TURP); findings need confirmation in additional RCTs to draw firmer conclusions regarding comparative effectiveness". This ECRI assessment states that "Additional independent RCTs would be useful to confirm comparative-effectiveness findings as well as compare AquaBeam with other BPH treatments. Three ongoing studies will partially address evidence gaps by reporting on 5-year outcomes and comparing Aquablation with HoLEP or transurethral laser enucleation".

The American Urological Association (AUA)'s guideline amendment on "Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia" (Parsons et al, 2020) noted that "Aquablation may be offered to patients with LUTS attributed to BPH provided prostate volume > 30 / < 80 g. (Conditional Recommendation; Evidence Level: Grade C)". Moreover, this recommendation is maintained in the AUA's guideline Part II on "Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: Surgical evaluation and treatment" (Lerner et al, 2021).

The Male Lower Urinary Tract Symptoms Committee (CTMH) of the French Urology Association (Lebdai et al, 2021) updated the guidelines for surgical and interventional management of benign prostatic obstruction (BPO). All available data published on PubMed between 2018 and 2020 were systematically searched and reviewed. All papers examining surgical and interventional management of adult patients with BPO were included for analysis. After studies critical analysis, conclusions with level of evidence and French guidelines were elaborated to address the pre-defined clinical questions. Updated guidelines and stated that "Aquablation and Rezum are under evaluation and should be offered in research protocols".

Sadri et al (2021) discussed the state of the literature regarding Aquablation, its limitations, and opportunities for its application in the treatment of BPEH. These researchers carried out a comprehensive review of original research on Aquablation. Articles related to TURP,

holmium laser enucleation of the prostate (HoLEP), Greenlight photo-selective vaporization of the prostate, and simple prostatectomy were reviewed for discussion. For small-medium prostates (30 to 80 ml), Aquablation's main advantages include better ejaculatory function and similar functional outcomes compared to TURP. For large prostates (80 to 150 ml), Aquablation demonstrated shorter operative time and superior ejaculatory function when compared to simple prostatectomy, HoLEP, and Greenlight PVP. Furthermore, Aquablation displayed shorter hospital stays than simple prostatectomy. The integration of software programming and semi-automatic technology increases the reproducibility of the procedure and aids in standardizing overall outcomes, while also accelerating the learning curve. Its ability to preserve antegrade ejaculation makes Aquablation a very compelling option for sexually active patients. However cost and post-operative bleeding risks remain a concern. The authors concluded that the current evidence suggests that Aquablation is a safe and effective alternative for BPH for small to large prostates. Moreover, these researchers stated that further prospective clinical trials, with comparisons to other BPH modalities, and data from longer follow-up periods are still needed.

Mullhaupt et al (2021) stated that a novel method for the surgical treatment of BPH called Aquablation has become commercially available; and HoLEP is a well-established procedure in the surgical treatment of BPH in prostate glands larger than 30 ml and a 1st-line therapy in glands over 80 ml. To-date, no data are available whether Aquablation is non-inferior compared with HoLEP in the treatment of patients with medium-to-large-sized prostates regarding safety and efficacy. These researchers presented the protocol of a study comparing Aquablation with HoLEP in the treatment of BPH in medium-to-large-sized prostates. This is a prospective, randomized, open-label, non-inferiority clinical trial conducted at a Swiss center of tertiary care. The primary outcome is assessment of non-inferiority of Aquablation compared with HoLEP in reducing LUTS due to BPO measured by the IPSS. Randomization will be carried out using secuTrial, stratifying on age (less than 70 years, 70+ years) and PV (less than 100 ml, 100+ ml). Both interventions are performed in an inpatient setting and regular follow-up controls starting 8 weeks after intervention and continuing up to 5 years will be performed. The primary outcome (change in IPSS from baseline to 6 months) will be tested for non-inferiority with a 1-sided t-test. Secondary outcomes, such

as efficacy parameters, several patient-reported outcome measures, and peri-procedural and safety parameters will be described by calculating means or relative frequencies for each treatment group and testing differences with 2-sided standard superiority tests. The authors concluded that the objective of this trial is to examine if Aquablation is a therapeutic option compared with HoLEP in patients with LUTS/BPO and medium-to-large-sized prostates, examining both short-term and long-term treatment effects as well as complications. By means of a prospective, randomized, non-inferiority trial design with clearly defined outcomes, as well as inclusion and exclusion criteria, and carried out according to well-defined quality standards, data will aid in better estimating treatment safety and efficacy of Aquablation. Furthermore, potential benefits as well as problems could be analyzed to show if Aquablation is potentially an equivalent alternative to HoLEP in the treatment of patients with medium-to-large-sized prostates, which would support the use of Aquablation in daily clinical practice.

Gilling, et al. (2022) reported on the 5-year outcomes of the double-blind, randomized controlled clinical trial of comparing Aquablation to TURP in 181 men with severe lower urinary tract symptoms secondary to benign prostatic hyperplasia. At 5 years, the International Prostate Symptom Score (IPSS) improved by 15.1 points in the Aquablation group and 13.2 points in TURP ($p = 0.2764$). However, for men with larger prostates (greater than or equal to 50 mL), IPSS reduction was 3.5 points greater across all follow-up visits in the Aquablation group compared to the TURP group ($p = 0.0123$). Improvement in peak urinary flow rate was 125 percent and 85 percent compared to baseline for Aquablation and TURP respectively. The risk of patients needing a secondary BPH medication or surgical intervention, up to 5 years due to lower urinary tract symptoms was 51 percent less in the Aquablation arm compared to the TURP arm.

An UpToDate review on “Surgical treatment of benign prostatic hyperplasia (BPH)” (McVary, 2021) states that “Robot-assisted waterjet ablation of the prostate is an emerging technique that uses an image-guided, robotically controlled waterjet, termed AquaBeam, to ablate prostatic tissue (Aquablation) … Aquablation may be used to treat LUTS/BPH in patients with a prostate volume between 30 and 80 g … At this time it is not clear whether Aquablation offers any advantages over existing technologies … It is not clear whether Aquablation offers

advantages over TURP in terms of impact on sexual function". Moreover, Aquablation is not mentioned in the "Summary and Recommendations" section of this UTD review.

CYP17 rs743572 Polymorphism in Benign Prostatic Hyperplasia

Weng and colleagues (2019) stated that many published studies have examined the association between CYP17 rs743572 polymorphism and BPH susceptibility but have yielded inconsistent results. These investigators carried out a meta-analysis using the multi-variate statistic method to address a more precise association. Case-control or cohort studies with adequate genotype distribution or minor allele frequency (MAF) were identified by searching the PubMed, Embase, and Web of Science databases up to December, 2018; ORs and 95 % CIs were calculated to estimate the association between CYP17 rs743572 polymorphism and BPH susceptibility. Pooled MAFs of 13 studies were 37 % in Caucasians and 56 % in Orientals, respectively. Pooled results of 8 studies suggested that CYP17 rs743572 was not associated with the BPH susceptibility in the overall population (OR = 0.98, 95 % CI: 0.80 to 1.20 for A2 versus A1; OR = 0.99, 95 % CI: 0.79 to 1.25 for A1/A2 versus A1/A1; OR = 0.97, 95 % CI: 0.62 to 1.53 for A2/A2 versus A1/A1). Sensitivity analysis showed the results were robust. Subgroup analysis based on ethnicity suggested that, in Orientals, A2 allele carriers had a 28 % lower risk of developing BPH compared with A1 allele carriers, and the risk of BPH is 47 % lower in A2/A2 genotype carriers compared with A1/A1 genotype carriers. No significant association was observed in Caucasians. The authors concluded that the findings of this study indicated a negative association between CYP17 and BPH in Orientals. However, due to limited sample size, the conclusion should be interpreted with caution and further studies with large sample size and high quality are needed.

Statins for the Treatment of BPH

In a meta-analysis, Yang and colleagues (2019) examined the relationship between statin with BPH and LUTS. These researchers carried out a systematic literature search using PubMed, Embase, Cochrane Library, Chinese Medical and Biological Literature Database, China HowNet, Vip, and Wanfang. They calculated pooled OR and 9%

CIs and SMD. Using Stata 12.0 and Review 5.3 for meta-analysis. This meta-analysis included 11 articles and 49,128 participants. Results showed statins could not reduce the incidence of BPH [OR= 0.77 (0.57 to 1.03, p= 0.08]. For patients over 60 years old, statins could reduce the incidence of BPH [OR= 0.35 (0.22 to 0.55), p< 0.0001]. Statins could slow down the progression of LUTS in BPH [SMD=-0.32 (-0.54 to -0.10), p= 0.004], but there is no significant correlation between them in patients taking drugs for less than 1 year. The authors concluded that statins have no significant effect on the incidence of BPH, but statins can reduce the risk of BPH for patients over 60 years old. For patients with hyperlipidemia, the duration of medication was more than 1 year, which could slow down the progression of LUTS. However, these researchers stated that more high-quality and large sample size studies are needed to further improve and verify.

The authors stated that this meta-analysis had several drawbacks. First, this review was limited to Chinese and English literature, so there is a possibility of publication bias. Second, the sample size of RCTs included in this meta was small, which may affect the generalization of the results. Third, LUTS progress evaluation only referred to IPSS score, but other quantitative indicators were not included because of the limitation of original literature data. Fourth, in an attempt to reduce or explain the high heterogeneity of the results, sensitivity analysis, and subgroup analysis were carried out. Despite subgroup analysis of age and duration of medication, heterogeneity remained high.

Virasoro and colleagues (2020) examined the safety and preliminary efficacy of the Optilume paclitaxel-coated balloon for the treatment of recurrent urethral stricture. Men with bulbar urethral strictures of less than or equal to 2 cm with 1 to 4 prior endoscopic treatments were enrolled at 4 study sites after ethics committee approvals. All subjects were treated with mechanical balloon dilation or direct visualization internal urethrotomy prior to drug-coated balloon treatment. Patients were evaluated at 2 to 5 days, 14 days, 3, 6, and 12-months post-treatment. The primary safety end-point was serious complications through 90 days post-procedure. The preliminary efficacy end-point was anatomic success, defined as urethral lumen of greater than or equal to 14-French at 12 months. A total of 53 subjects were enrolled and treated; 46 completed the 12-month follow-up; 43 % of men had undergone

greater than 1 previous dilation; the mean for the overall study population was 1.7 prior dilations. There were no serious AEs related to the treatment within 90 days. Anatomic success was achieved in 32/46 (70 %; 95 % CI: 54 to 82 %) at 12 months. The 14 failures included 7 cystoscopic recurrences, 5 re-treatments, and 2 patients who exited the study early due to symptom recurrence. The authors concluded that the 1-year data indicated that the Optilume paclitaxel-coated balloon was safe for the treatment of recurrent bulbar urethral strictures. These researchers stated that early efficacy results were encouraging and supported further follow-up of these men through 5 years, as well as further investigation with a randomized trial.

Mangir and Chapple (2020) stated that a recent development in the prevention of the recurrence of urethral stricture following direct vision internal urethrotomy (DVIU) is the commercialization of a drug-coated balloon catheter (Optilume), which combines a balloon dilation technique and drug delivery. The highly lipophilic drug, paclitaxel, is released after balloon dilatation, limiting hyperactive cell proliferation and fibrotic scar formation. Paclitaxel is an anti-neoplastic drug that inhibits cell replication by stabilizing intracellular microtubules. Paclitaxel is thought to inhibit the proliferation of ureteral smooth muscle cells and urothelial cells. The distribution of paclitaxel in the urothelial, submucosal, and smooth muscle layers has previously been demonstrated in a porcine model after ureteral dilatation, showing reduced inflammation with drug-eluting balloons. The pseudo-stratified epithelium of the urethral mucosa has also been shown to allow the distribution of paclitaxel in the muscular layer in a rabbit model. Nevertheless, there is no direct evidence to suggest an effect of paclitaxel on urethral stricture. This technology is now undergoing clinical trials. The interim results of the first non-randomized clinical trial with 53 patients showed that such an approach could be used safely in the treatment of short bulbar urethral stricture with an anatomical success rate of 70 % at 12 months (Virasoro et al, 2020). The authors concluded that the safety and efficacy of the Optilume paclitaxel-coated balloon will need to be studied in RCTs with long-term follow-up.

Furthermore, an UpToDate review on "Surgical treatment of benign prostatic hyperplasia (BPH)" (McVary, 2020) does not mention drug-coated balloon as a management / therapeutic option.

Melatonin

In a randomized clinical trial, Fotovat and colleagues (2021) examined the effect of melatonin along with tamsulosin in improving the BPH urinary symptoms. A total of 108 men with BPH symptoms, age of greater than or equal to 50 years, and IPSS of greater than or equal to 8 entered into the parallel group randomized, double-blind clinical trial with balanced randomization. Treatment group received of 3-mg melatonin plus 0.4-mg tamsulosin and control group received placebo plus 0.4-mg tamsulosin. Patients and physicians were concealed by sealed and opaque envelopes. Symptoms were evaluated at baseline and 1 month after treatment. All scores at the initial and end of the study were compared and analyzed using SPSS software. This study showed that the addition of melatonin to classic treatment of BPH patients with tamsulosin could significantly reduce the likelihood of nocturia by 2.39 times (95 % CI: 1.07 to 5.32, OR = 2.39, p = 0.033) and could also reduce the frequency of urination by 2.59 times (95 % CI: 1.15 to 5.84, OR = 2.59, p = 0.021). There was no statistically significant difference between the 2 groups in IPSS, intermittency, incomplete emptying, straining, urgency, and weak stream. The authors concluded that melatonin plus tamsulosin treatment was associated with a significant improvement of nocturia and frequency in patients with BPH; however, more studies are needed to confirm these preliminary findings.

XFLO Expander System (Mercury Expander System)

Chughtai and colleagues (2021) examined the safety, feasibility, and tissue response of a novel device for the treatment of LUTS secondary to BPH, using the 1st-generation XFLO Expander System (Mercury Expander System). The implant was deployed and retrieved using flexible cystoscope in 8 adult male canines, separated into 3 study arms by retrieval date (1-, 6-, and 12- months post-deployment). Cystoscopy and urethrograms verified implant position/diameter; bladder neck and external sphincter function/changes; prostatic tissue response; and implant condition. One-month post-retrieval, the prostate and surrounding tissue was sectioned and evaluated by a veterinary pathologist. All implants were successfully deployed in the prostatic urethra. Urethral width was increased (6.9 ± 1.8 mm to 10.2 ± 0.6 mm, p

= 0.012) and preserved through the dwell period. Urethral length and sphincter diameters did not significantly change. All subjects (n = 8) remained continent without obstruction or retention; AEs included incisional site bleeding (n = 2) and transient hematuria (n = 3). One implant migrated into the bladder and spontaneously re-positioned into the prostatic urethra. Post-retrieval, explant surfaces demonstrated no tissue growth, encrustation or stone formation. Imaging revealed contact site erythema and indentation, but no stones, strictures, perforations, erosions, nor ulcerations. Histopathology revealed glandular acinar changes, inflammation, and fibrosis. The authors concluded that the XFLO Expander System demonstrated a favorable safety profile in the canine model. Changes in the prostatic urethra shape were noted with an increase in urethral width during the dwell period with minimal tissue changes. Furthermore, the implant did not demonstrate any encrustation, tissue growth or stone formation.

CPT Codes/ HCPCS Codes/ICD-10 Codes
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+"

Code	Code Description
CPT codes covered if selection criteria are met:	
52282	Cystourethroscopy, with insertion of permanent urethral stent
52441	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant
52442	each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)
52450	Transurethral incision of prostate
52601	Transurethral electrosurgical resection of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included) [laser prostatectomy]

Code	Code Description
52647	Laser coagulation of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included if performed)
52648	Laser vaporization of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, internal urethrotomy and transurethral resection of prostate are included if performed) [TUVP]
52649	Laser enucleation of the prostate with morcellation, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, internal urethrotomy and transurethral resection of prostate are included if performed) [not covered for bipolar plasma enucleation]
53850	Transurethral destruction of the prostate tissue; by microwave thermotherapy [TUMT]
53854	Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy
CPT codes not covered for indications listed in the CPB	
Prosta-Seq, seminal cell free DNA concentration, measurement of blood-based microRNAs, Histotripsy, Phytotherapy (e.g., African plum tree bark, pumpkin seeds, rye pollen, saw palmetto, South African star grass roots, and Stinging nettle roots), Rezum system, CYP17 rs743572 polymorphism testing - no specific code	
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)
0619T	Cystourethroscopy with transurethral anterior prostate commissurotomy and drug delivery, including transrectal ultrasound and fluoroscopy, when performed

Code	Code 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 (e.g., congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction [PAE]
53855	Insertion of a temporary prostatic urethral stent, including urethral measurement
55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance for interstitial cryosurgical probe placement)
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
Other CPT codes related to the CPB	
52281	Cystourethroscopy, with calibration and/or dilation of urethral stricture or stenosis, with or without meatotomy, with or without injection procedure for cystography, male or female
53000 - 53010	Urethrotomy or urethrostomy, external (separate procedure)
53600 - 53621	Dilation of urethral stricture
HCPCS codes covered if selection criteria are met	
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	4 or more implants
HCPCS codes not covered for indications listed in the CPB	
C2625	Stent, noncoronary, temporary, with delivery system [urethral stent]
C9769	Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J3315	Injection, triptorelin pamoate, 3.75 mg
J9155	Injection, Degarelix, 1 mg

Code	Code Description
J9202	Goserelin acetate implant, per 3.6 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
J9218	Leuprolide acetate, per 1 mg
J9219	Leuprolide acetate implant, 65 mg
J9226	Histrelin implant (Supprelin LA), 50 mg
S0090	Sildenafil citrate, 25 mg
ICD-10 codes covered if selection criteria are met	
N35.010 - N35.92	Urethral stricture
N40.0 - N40.1	Enlarged prostate (EP)
N40.2 - N40.3	Nodular prostate
ICD-10 not codes covered if selection criteria are met	
C61	Malignant neoplasm of prostate [not covered for Prosta-Seq test and measurement of seminal cell free DNA concentration]

The above policy is based on the following references:

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Amendment to Aetna Clinical Policy Bulletin Number: 0079 Benign Prostatic Hyperplasia

There are no amendments for Medicaid.

Revised 04/26/2022