Medical Policy

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Title: Prostatic Urethral Lift

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Populations	Interventions	Comparators	Outcomes
Individuals: • With lower urinary tract obstruction symptoms due to benign prostatic hyperplasia	Interventions of interest are: • Prostatic urethral lift	Comparators of interest are: • Transurethral resection of the prostate • Minimally invasive prostate resection or ablation • Continued medical management	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

DESCRIPTION

Benign prostatic hyperplasia (BPH) is a common condition in older individuals that can lead to increased urinary frequency, an urgency to urinate, nocturia, a hesitancy to urinate, and a weak stream when urinating. The prostatic urethral lift (PUL) procedure involves the insertion of one or more permanent implants into the prostate, which retract prostatic tissue and maintain an expanded urethral lumen.

OBJECTIVE

The objective of this policy is to determine whether prostatic urethral lift improves the net health outcome in individuals with benign prostatic hyperplasia.

BACKGROUND

Benign Prostatic Hyperplasia

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

Two scores are widely used to evaluate BPH-related symptoms. The American Urological Association Symptom Index (AUASI) is a self-administered 7-item questionnaire assessing the severity of various urinary symptoms.[2] Total AUASI scores range from 0 to 35, with overall severity categorized as mild (≤7), moderate (8-19), or severe (20-35).[1] The International Prostate Symptom Score incorporates questions from the AUASI and a quality of life question or "Bother score."[3]

Management

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

Medical Therapy

A discussion about medical therapy is generally indicated for patients with moderate-to-severe symptoms (eg, AUASI score, ≥8), bothersome symptoms, or both. Available medical therapies for BPH-related lower urinary tract dysfunction include α-adrenergic blockers (eg, alfuzosin, doxazosin, tamsulosin, terazosin, silodosin), 5α-reductase inhibitors (eg, finasteride, dutasteride), combination α-adrenergic blockers and 5α-reductase inhibitors, anti-muscarinic agents (eg, darifenacin, solifenacin, oxybutynin), and phosphodiesterase-5 inhibitors (eg, tadalafil).[1] A 1999 meta-analysis of both indirect comparisons from placebo-controlled studies (including 6333 patients) and direct comparative studies (including 507 patients) found that the IPSS improved by 30% to 40% and the Qmax score (mean peak urinary flow rate) improved by 16% to 25% in individuals assigned to α-adrenergic blockers.[4] Combination therapy using an α-adrenergic blocker and 5α-reductase inhibitor has been shown to be more effective for improving IPSS than either treatment alone, with median scores improving by more than 40% over 1 year and by more than 45% over 4 years.[5]

Surgical and Ablative Therapies

Patients who do not have sufficient response to medical therapy, or who are experiencing significant side effects with medical therapy, may be referred for surgical or ablative therapies. Various surgical or ablative procedures are used to treat BPH. Transurethral resection of the prostate is generally considered the reference standard for comparisons of BPH procedures.[6] In the perioperative period, transurethral resection of the prostate is associated with risks of any operative procedure (eg, anesthesia risks, blood loss). Although short-term mortality risks are generally low, 1 large prospective study with 10,654 patients reported the following short-term complications: "failure to void (5.8%), surgical revision (5.6%), significant urinary tract infection (3.6%), bleeding requiring transfusions (2.9%), and transurethral resection syndrome (1.4%)."[7] Incidental carcinoma of the prostate was diagnosed by histologic examination in 9.8% of patients. In the longer term, transurethral resection of the prostate is associated with increased risk of sexual dysfunction and incontinence.

Several minimally invasive prostate ablation procedures have also been developed, including transurethral microwave thermotherapy, transurethral needle ablation of the prostate, urethromicroablation phototherapy, and photoselective vaporization of the prostate. The minimally invasive procedures were individually compared with transurethral resection of the prostate at the time they were developed, which provided a general benchmark for evaluating those procedures.

REGULATORY STATUS

One implantable transprostatic tissue retractor system has been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. In December 2013, the NeoTract UroLift® System UL400 (NeoTract, Pleasanton, CA) was cleared (after receiving clearance through FDA's de novo classification process in March 2013; K130651/DEN130023). In March 2016, FDA determined that the UL500 was substantially equivalent to existing devices (UL400) for the treatment of symptoms of urinary flow obstruction secondary to benign prostatic hyperplasia in individuals age 50 years and older. In 2017, FDA expanded the indication for the UL400 and UL500 to include *lateral and median* lobe hyperplasia in men 45 years or older. FDA product code: PEW.

POLICY

A. Use of prostatic urethral lift in individuals with moderate-to-severe lower urinary tract obstruction due to benign prostatic hyperplasia may be considered **medically necessary** in individuals 45 years of age or older when ALL of the following criteria are met:

   1. The patient has persistent or progressive lower urinary tract symptoms despite medical therapy (α_1-adrenergic antagonists maximally titrated, 5α-reductase inhibitors, or combination medication therapy maximally titrated) over a trial period of no less than 6 months, or is unable to tolerate medical therapy; AND

2. Prostate gland volume is ≤80 mL; AND

3. Patient does not have urinary tract infection or recent prostatitis (within past year); AND

4. Patient does not have prostate-specific antigen level ≥3 ng/mL, or has had appropriate testing to exclude diagnosis of prostate cancer; AND

5. Patient does not have a contact dermatitis nickel allergy.

B. The prostatic urethral lift procedure in other situations is considered **experimental / investigational**.

RATIONALE

This evidence review was created in August 2015 and has been updated regularly with literature search of the MEDLINE database through June 4, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Prostatic Urethral Lift

Clinical Context and Therapy Purpose

The purpose of prostatic urethral lift (PUL) in patients who have lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) is to provide a treatment option that is an alternative to or an improvement on existing therapies such as medical management or transurethral resection of the prostate (TURP).

The question addressed in this evidence review is: Does PUL improve the net health outcome in individuals with BPH?

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

Patients
The relevant population of interest is men who are experiencing lower urinary tract symptoms without a history suggesting non-BPH causes of the symptoms and who do not have sufficient response to medical therapy or are experiencing significant side effects with medical therapy.

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

One device, the NeoTract UroLift System, has been cleared for marketing by the U.S. Food and Drug Administration (see Regulatory Status section). The device has 2 main components: the delivery device and the implant. Each delivery device comes preloaded with a UroLift implant.

Comparators
Various surgical or ablative procedures are used to treat BPH. TURP is generally considered the reference standard for comparisons of BPH procedures. Several minimally invasive prostate ablation procedures have also been developed, including transurethral microwave thermotherapy, transurethral needle ablation of the prostate, urethromicroablation phototherapy, and photoselective vaporization of the prostate.

Outcomes
A number of health status measures are used to evaluate symptoms relevant to BPH and adverse events of treatment for BPH, including urinary dysfunction measured by urinary flow rate (Qmax), ejaculatory dysfunction, overall sexual health, and overall quality of life. Some validated patient-reported scales are shown in Table 1.

Of note, prostate volume does not have a direct correlation with severity of urinary symptoms.[8]

Table 1. Patient-Reported Health Outcome Measures Relevant to Benign Prostatic Hyperplasia

Measure	Outcome Evaluated	Description	Clinically Meaningful Difference (If Known)
Male Sexual Health Questionnaire for Ejaculatory Dysfunction[9]	Ejaculatory function and quality of life	Patient-administered, 4-item scale. Symptoms rated as absent (15) to severe (0). QOL assessed as no problem (0) to extremely bothered (5).	
Sexual Health Inventory for Men[10]	Erectile function	Patient-administered, 5-item scale. Erectile dysfunction rated as severe (1-7), moderate (8-11), mild to moderate (12-16), or mild (17-21). Fewest symptoms present for patients with scores 22-25.	5-point change[11]
American Urological Association Symptom Index; International Prostate Symptom Score[1,3,12]	Severity of lower urinary tract symptoms	• Patient-administered, 7-item scale. Symptoms rated as mild (0-7), moderate (8-19), or severe (20-35) • IPSS asks an additional question, rating QOL as delighted (0) to terrible (6)	• Minimum of 3-point change[1,12] • Minimum of 30% change[13]

Measure	Outcome Evaluated	Description	Clinically Meaningful Difference (If Known)
Benign Prostatic Hyperplasia Impact Index[14,15]	Effect of urinary symptoms on health domains	Patient-administered, 4-item scale. Symptoms rated as absent (0) to severe (13).	Minimum of 0.4-point change[12]

QOL: quality of life.

Timing

Outcomes data demonstrating durability to at least 2 years is preferred.

Setting

Medical management of BPH may occur in the primary or secondary care setting. Men needing surgical management are referred to urologists with experience in surgical procedures for treating BPH.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Several systematic reviews on PUL have been published. They include a similar set of trials and noncomparative studies. For example, Perera et al (2015) reported on the results of a systematic review and meta-analysis[16] of studies reporting outcomes after the PUL procedure, which included 7 prospective cohort studies,[17-23] a crossover study (Cantwell et al [2014][24]), and the LIFT RCT (Roehrborn et al [2013],[25] McVary et al [2014][26]). The pooled standardized mean gain estimates for prostate symptoms scores (International Prostate Symptom Score [IPSS], Benign Prostatic Hyperplasia Impact Index [BPH-II]), and sexual health scores used responses from 452 to 680 patients. The standardized mean gain for prostatic symptoms scores ranged from -1.3 (95% confidence interval [CI], -1.4 to -1.2) to -1.6 (95% CI, -1.7 to -1.3), which translated into a clinically meaningful improvement. The standardized mean gain for sexual health scores ranged from 0.3 (95% CI, 0.2 to 0.4) to 0.4 (95% CI, 0.3 to 0.5), suggesting a small improvement.

Shore (2015)[27] performed a systematic review of UroLift studies, which included the LIFT RCT (Roehrborn et al [2013][25]; Roehrborn et al [2015][28]; McVary et al [2014][26]), a crossover study (Cantwell et al [2014][24]), and 4 prospective cohort studies (Garrido Abad et al [2013][17]; Chin et al [2012][21]; Woo et al [2012][22]; McNicholas et al [2013][20]). Only data that showed absolute change, supported by a 95% CI or standard deviation, were included in the weighted analysis. Reviewers reported that, from 0.5 to 1.5 months to 2 years, mean peak urinary flow rate (Qmax) increased from 3.3 to 4.15, IPSS improved from -4.5 to -9.2 relative to baseline, quality of life improved from -1.2 to -2.2 relative to baseline, and BPH-II scores improved from -0.1 to -3.8 relative to baseline. Changes in postvoid residual volume were not statistically significant.

Jones et al (2016) performed a systematic review of UroLift studies with at least 12 months of follow-up.[29] Seven studies were identified, which included 4 noncomparative studies (Woo et al [2011],[23] Chin et al [2012],[21] McNicholas et al [2013],[20] Bozkurt et al [2016][30]), a crossover study (Cantwell et al [2014][24]), and 2 RCTs (LIFT[25] and BPH6[11]). Reviewers included data from 440 patients. Only the data from men in the UroLift arms of these RCTs were included. Results were combined to create summaries, but the meta-analytic methods used to combine the data were not described, and precision estimates were not given. Reviewers reported that Qmax increased from 8.4 mL/s to 11.8 mL/s, mean IPSS improved from 24.1 to 14, mean quality of life improved from 4.5 to 2.3, and mean 5-item International Index of Erectile Function score improved from 17.7 to 18.2. The most frequent complications reported were dysuria, hematuria, and pelvic pain.

The National Institute for Health and Care Excellence (2016) published a technical guidance on prostatic lift procedures.[31] The National Institute for Care Excellence performed a literature search and data synthesis to support the development of the guidance. Studies selected were the same studies included in Perera et al (2015),[16] except for the exclusion of Hoffman et al (2012)[18] and the inclusion of Garrido Abad et al (2013)[17] in the analysis. Comparators for the review were TURP and holmium laser enucleation of the prostate (HoLEP). When the literature search was performed, there were no studies directly comparing PUL with either TURP or HoLEP. Therefore, the Institute extracted data from a TURP vs HoLEP systematic review to perform a "pragmatic indirect comparison" of these comparators with prostatic lift procedures. Reviewers concluded that while PUL provided a significant improvement in IPSS, BPH-II, and quality of life, those improvements were smaller than those seen with TURP or HoLEP; however, it should be noted that the PUL procedure was associated with a slight improvement in erectile or ejaculatory function.

Randomized Controlled Trials

Two RCTs of PUL have been performed. Key trial characteristics and study results are shown below in Tables 2 and 3. Additionally, a brief description of each trial is provided in the following sections.

Table 2. PUL Randomized Controlled Trial Characteristics

						Interventions, n	
Study; Trial	**Countries**	**Sites**	**Dates**	**Inclusion Criteria**	**Baseline Prostate Volume, cm^3**	**Active**	**Comparator**
Sonksen et al (2015)[11]; BPH6	Denmark, Germany, U.K.	10	Feb 2012-Oct 2013	Age ≥50 y, IPSS >12, prostate volume ≤60 cm^3	16-59	PUL=46	TURP=45
Roehrborn et al (2013)[25]; LIFT	U.S., Canada, Australia	19	Feb-Dec 2011	Age ≥50 y, IPSS ≥13, prostate volume 30-80 cm^3, washed out of BPH medications	30-77	PUL=140	Sham=66

BPH: benign prostatic hypertrophy; IPSS: International Prostate Symptom Score; PUL: prostatic urethral lift; TURP: transurethral resection of the prostate.

BPH6 Study

Sonksen et al (2015) reported on the results of a multicenter RCT comparing the PUL procedure with TURP among individuals ages 50 and older with lower urinary tract symptoms, secondary to benign prostatic obstruction.[11] Eligible patients had an IPSS above 12, a Qmax of 15 mL/s or less for a 125-mL voided volume, a postvoid residual volume less than 350 mL, and prostate volume of 60 cm^3 or less on ultrasound. Patients were excluded if there was median lobe obstruction in

the prostate or signs of active infection. The trial used a novel composite end point, referred to as the BPH6, which included the following criteria:

- Lower urinary tract symptom relief: Reduction in IPSS by ≥30% within 12 months, relative to baseline
- Recovery experience: Self-assessed by patients as ≥70% within 1 month, using a visual analog scale
- Erectile function: Reduction in Sexual Health Inventory for Men (SHIM) score by ≤6 points within 12 months, relative to baseline
- Ejaculatory function: Emission of semen as assessed by question 3 in the Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD)
- Continence preservation: Incontinence Severity Index ≤4 points at all follow-up visits
- Safety: No treatment-related adverse events exceeding grade 1 on the Clavien-Dindo classification system at time or procedure or any follow-up.

Patients were considered treatment responders if they met all 6 composite criteria. While this composite end point has not been previously validated, core components of the composite score have been independently validated in a clinical setting. The trial used a noninferiority design with a margin of 10% for the primary end point, BPH6. Study investigators modified 2 of the original end point definitions in the study's analysis, including changing the sexual function element assessment from a single time point (12 months) to assess sustained effects during 12 months of follow-up, and lowering the threshold of quality of recovery on a visual analog scale from 80 to 70.

Table 3. Summary of Evidence from the BPH6 Study

Outcomes	3 Months		12 Months		24 Months	
	PUL	TURP	PUL	TURP	PUL	TURP
Mean change in IPSS						
n	42	34	40	32	37	32
Mean (SD)	-11.7 (8.5)	-11.8 (9.5)	-10.9 (7.9)	-15.4 (6.8)	-9.2 (9.2)	-15.3 (7.5)
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Comparison (p)	0.978		0.013		0.004	
Change in IPSS QOL						
n	43	34	40	32	37	32
Mean (SD)	-2.6 (1.7)	-2.4 (2.0)	-2.8 (1.8)	-3.1 (1.6)	-2.5 (1.8)	-3.3 (1.6)
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Comparison (p)	0.55		0.436		0.066	
Change in Qmax						
n	33	25	32	29	27	27
Mean (SD)	4.2 (5.0)	12.7 (9.8)	4.0 (4.8)	13.7 (10.4)	5.0 (5.5)	15.8 (16.5)
p	<0.001	0.003	<0.001	0.003	<0.001	0.002
Comparison (p)	<0.001		<0.001		0.002	
Change in SHIM score						
n	38	27	32	27	29	28
Mean (SD)	-0.7 (5.2)	-1.0 (5.2)	-0.1 (4.7)	-0.9 (4.3)	-0.2 (4.3)	-1.8 (4.90)
p	0.386	0.328	0.940	0.29	0.832	0.067
Comparison (p)	0.861		0.486		0.201	
Change in MSHQ-EjD function score						
n	38	27	32	27	29	27
Mean (SD)	-0.7 (2.1)	-3.0 (4.1)	1.3 (3.3)	-3.7 (4.1)	0.3 (3.4)	-4.0 (4.6)
p	0.251	<0.001		<0.001	0.666	<0.001
Comparison (p)	<0.001		<0.001		<0.001	
Change in MSHQ-EjD bother score						
n	38	28	32	27	29	27
Mean (SD)	-0.7 (2.1)	0.2 (1.5)	0.5 (2.2)	0.0 (1.5)	-0.1 (2.2)	-0.3 (1.9)

Outcomes	3 Months		12 Months		24 Months	
p	0.062	0.470	0.214	0.896	0.734	0.415
Comparison (p)	0.069		0.359		0.771	
Composite score	NR	NR	Response: 52%	Response: 20%	NR	NR
Comparison (95% CI); p	NR		Difference: 32% (10% to 51%); 0.005		NR	
Clavien-Dindo adverse events						
Grade 1, n (%)	NR	NR	30 (68)	26 (74)	NR	NR
Adverse events			60	79		
Grade 2, n (%)	NR	NR	3 (7)	4 (11)	NR	NR
Adverse events			3	5		
Grade 3, n (%)	NR	NR	4 (9)	5 (14)	NR	NR
Adverse events			4	5		

Adapted from Gratzke et al (2017).[32]
BPH: benign prostatic hypertrophy; CI: confidence interval; IPSS: International Prostate Symptom Score; MSHQ-EjD: Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NR: not reported; PUL: prostatic urethral lift; Qmax: mean peak urinary flow rate; QOL: quality of life; SD: standard deviation; SHIM: Sexual Health Inventory for Men; TURP: transurethral resection of the prostate.

Ninety-one patients were randomized to TURP (n=45) or PUL (n=46). Ten patients in the TURP group and 1 patient in the PUL group declined treatment, leaving an analysis group of 80 subjects. The analysis was per-protocol, including 35 in the TURP group and 44 in the PUL group (87% of those randomized; 1 patient was excluded for violating the active urinary retention exclusion criterion). Groups were similar at baseline, except for the MSHQ-EjD function score. For procedure recovery, 82% of the PUL group achieved the recovery end point by 1 month compared with 53% of the TURP group (p=0.008). For the study's primary outcome, the proportion of participants who met the original BPH6 primary end point was 34.9% for the PUL group, and 8.6% for the TURP group (noninferiority p<0.001; superiority p=0.006). The modified BPH6 primary end point was met by 52.3% of the PUL group and 20.0% of the TURP group (noninferiority p<0.001; superiority p=0.005). Both groups demonstrated improvements over IPSS, IPSS quality of life score, BPH-II score, and Qmax over time, as described in Table 3. There were 60 grade 1 adverse events in 30 (68%) PUL patients and 79 adverse events in 26 (74%) TURP patients. The number of patients experiencing grade 2 and 3 adverse events was similar between groups. Intention-to-treat analyses were not reported.

Gratzke et al (2017) reported on 2-year results from BPH6.[32] Two additional patients were excluded from analysis: 1 TURP patient who discontinued participation; and 1 PUL patient who had a protocol violation. Composite scores for the 2 groups were not reported. Both groups continued to show significant improvements in IPSS score, IPSS quality of life, BPH-II score, and Qmax during the 2-year follow-up, as described in Table 3. Six (14%) PUL patients and 2 (6%) TURP patients had secondary treatment (PUL, intradetrusor botulinum toxin, laser or TURP procedure), showing moderate durability over 2 years.

The purpose of the gaps tables (see Tables 4 and 5) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 4. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
BPH6	3. Unclear history of BPH treatments				
LIFT	3. Unclear history of BPH treatments				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
BPH: benign prostatic hypertrophy.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
BPH6		1. Blinding not feasible		6. Only per-protocol analysis presented		
LIFT				1, 2, 5. High losses and/or exclusions in extended follow-up, only LOCF sensitivity analyses provided		3, 4. CI not reported for treatment effects

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval; LOCF: last observation carried forward.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Subsection Summary - BPH6 Study: In the BPH6 study, PUL was both noninferior ($p<0.001$) and superior ($p=0.005$) to TURP for the study's composite end point. This end point was calculated using the concurrent achievement of validated measures of symptoms and complications and is sufficient to describe patient health outcomes. TURP was associated with greater improvements in urinary tract obstruction symptom outcomes and with greater declines in ejaculatory function compared with PUL.

LIFT Study

Comparative Data: Roehrborn et al (2013) reported on results of the pivotal LIFT study, an RCT comparing PUL with sham control among 206 individuals ages 50 and older with lower urinary tract symptoms secondary to BPH.[25] Eligible patients had an American Urological Association Symptom Index (AUASI) score of 13 or greater, Qmax of 12 mL/s or less for a 125-mL voided volume, and a prostate volume between 30 and 80 mL. Patients were excluded if there was median lobe obstruction in the prostate, postvoid obstruction of more than 250 mL, or signs of active infection. Patients underwent washout of BPH medications before enrollment; the washout period was 2 weeks for α-blockers and 3 months for 5α-reductase inhibitors. Patients were randomized to PUL (n=140) or sham control (n=66) and evaluated at 3 months postprocedure for the trial's primary efficacy end point. After that, all patients were unblinded, and sham control

patients were permitted to undergo the PUL procedure. Fifty-three control subjects eventually underwent a PUL procedure. The analysis was intention-to-treat. The study met its primary efficacy end point, which was that the reduction in AUASI score at 3 months postprocedure had to be at least 25% greater after the PUL than the reduction in AUASI score seen with sham (p=0.003). The AUASI score decreased from 24.4 at baseline to 18.5 at 3-month follow-up for sham control patients and from 22.2 at baseline to 11.2 at 3-month follow-up for PUL patients (see Table 6). The 3-month change in Qmax was 4.28 mL/s for PUL patients and 1.98 mL/s for sham control patients (p=0.005). Compared with sham control patients, PUL patients had greater improvements in quality of life scores and BPH-II score (see Table 7). Nine serious adverse events in 7 patients were reported in the PUL group, and 1 serious adverse event was reported in the sham group during the first 3 months of follow-up. Limitations in trial design are summarized in Tables 4 and 5.

McVary et al (2014) reported on sexual function outcomes in a subset of patients from the LIFT study.[26] At baseline, 53 (38%) PUL subjects and 23 (53%) sham control subjects were sexually inactive or had severe erectile dysfunction and were censored from the primary sexual function analysis. Scores on the SHIM, MSHQ-EjD function scale and the MSHQ-EjD bother scale did not differ significantly between groups.

Table 6. Summary of LIFT Initial Trial Results

Study	Change in IPSS	Change in IPSS QOL	Change in Qmax	Change in MSHQ-EjD Function	Change in MSHQ-EjD Bother	Any Adverse Events, n (%)	Serious Adverse Events, n (%)
LIFT							
N at 3 months	206	206	182	144	177	206	206
PUL	-11.1 (7.7)	-2.2 (1.8)	4.3 (5.2)	2.2 (2.5)	-0.8 (1.5)	122 (87%)	7 (5%)
Adverse events						268	9
Sham	-5.9 (7.7)	-1.0 (1.5)	2.0 (4.9)	1.7 (2.6)	-0.7 (1.6)	43 (52%)	1 (1.5%)
Adverse events						53	1
TE (p)	NR (0.003)	NR (<0.001)	NR (0.005)	NR (0.283)	NR (0.60)	NR	NR

Adapted from Roehrborn et al (2013).[25]
Values are mean (standard deviation) unless otherwise indicated.
IPSS: International Prostate Symptom Score; MSHQ-EjD: Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NR: not reported; PUL: prostatic urethral lift; Qmax: mean peak urinary flow rate; QOL: quality of life; TE: treatment effect.

Table 7. Summary of Evidence for LIFT Study, Including Participants in the PUL Group

Outcomes	3 Months	1 Year	2 Years	3 Years	5 Years
N	140	129	118	109	87
Death/LTFU	0	2	7	2	18
Protocol deviations	3	0	0	1	0
Retreatment	0	6	4	6	4
Change in IPSS					
n	136	123	103	93	72
Change	-11.14 (7.72)	-10.61 (7.51)	-9.13 (7.62)	-8.83 (7.41)	-35.9%
95% CI	-12.45 to -9.83	-11.95 to -9.27	-10.62 to -7.64	-10.35 to -7.30	-44.4% to -27.3%
p	<0.001	<0.001	<0.001	<0.001	<0.001
Change in IPSS QOL					

Outcomes	3 Months	1 Year	2 Years	3 Years	5 Years
n	136	123	103	93	72
Change	-2.22 (1.78)	-2.31 (1.60)	2.19 (1.72)	-2.25 (1.72)	-50.3
95% CI	-2.52 to -1.92	-2.59 to -2.02	-2.53 to -1.86	-2.60 to -1.89	-58.4% to -42.2%
p	<0.001	<0.001	<0.001	<0.001	<0.001
Change in Qmax					
n	122	102	86	69	52
Change	4.29 (5.16)	4.03 (4.96)	4.21 (5.09)	3.47 (5.00)	44.3%
95% CI	3.36 to 5.21	3.06 to 5.00	3.12 to 5.30	2.27 to 4.67	29.4% to 59.1%)
p	<0.001	<0.001	<0.001	<0.001	<0.001
Change in SHIM score					
n	91	87	72	66	NR
Change	1.27 (4.65)	0.70 (5.12)	1.06 (4.78)	0.53 (4.41)	NR
95% CI	0.31 to 2.24	-0.39 to 1.79	-0.07 to 2.18	-0.55 to 1.62	NR
p	0.005	0.299	0.046	0.338	NR
Change in MSHQ-EjD function score					
n	91	87	72	66	49
Change	2.31 (2.58)	1.56 (2.68)	1.08 (2.51)	0.56 (2.48)	9.3%
95% CI	1.77 to 2.85	0.99 to 2.13	0.49 to 1.67	-0.05 to 1.17	-3.8% to 22.5%
p	<0.001	<0.001	<0.001	0.013	0.096
Change in MSHQ-EjD bother score					
n	91	87	72	66	49
Change	-1.07 (1.44)	-0.76 (-1.55)	0.63 (1.51)	-0.59 (1.52)	-6.3%
95% CI	-1.37 to -0.77	-1.09 to -0.43	-0.98 to -0.27	-0.96 to -0.22	-31.5% to 18.8%
p	<0.001	<0.001	<0.001	<0.001	0.019

Adapted from Roehrborn et al (2015)[28] for data from 3 months to 3 years and Roehrborn et al (2017)[33] for data for 5 years.
While not specifically indicated, change values likely represent means and standard deviations.
CI: 95% confidence interval; IPSS: International Prostate Symptom Score; LTFU: lost to follow-up; MSHQ-EjD: Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NR: not reported; PUL: prostatic urethral lift; Qmax: mean peak urinary flow rate; QOL: quality of life; SHIM: Sexual Health Inventory for Men.

Follow-Up of Sham-Assigned Crossover Participants: Cantwell et al (2014) reported on 12-month outcomes for 53 subjects in the LIFT sham control group who underwent PUL after unblinding at 3 months postprocedure.[24] Crossover (unblinded) patients had a change in IPSS from 23.4 to 12.3 at 3 months postprocedure compared with the change in IPSS from 25.2 to 20.2 at 3 months after the sham procedure. Subjects had greater improvements in BPH-II score in the crossover period (-3.3) than in the sham period (-1.9; p=0.024) but did not report significant differences in improvement in Qmax. Change in sexual function scores did not differ significantly after the sham procedure compared with after active procedure.

Rukstalis et al (2016) reported on 24-month outcomes for 42 of the 53 participants in the LIFT sham group who underwent PUL after unblinding.[34] During the 24 months, 4 patients were known to have had TURP, and 1 patient required additional PUL implants. The change in IPSS from baseline to 24 months was -9.6 (-35%; 95% CI, not reported; p<0.001) and there were significant score improvements in Qmax, BPH-II scores, and quality of life. There were no significant changes compared with baseline for SHIM scores; however, MSHQ-EjD scores improved by 41% (p<0.001).

Follow-Up of PUL-Assigned Participants: Roehrborn et al (2015) reported on 3-year results from patients randomized to PUL in the LIFT study.[28] After exclusion of 11 subjects who were lost to follow-up, 36 subjects with missing data, protocol deviations, medication treatment for BPH, or other prostate procedures, and 15 subjects who underwent surgical retreatment for lower urinary tract symptoms (6 with repeat PUL procedures, 9 with TURP or laser vaporization), the 3-year effectiveness analysis included 93 (66%) of the original 140 subjects. For subjects with follow-up

data, change in IPSS was -8.83 (95% CI, -10.35 to -7.30; p<0.001). Significant improvements were also reported for the quality of life score, BPH-II score, and Qmax. Sexual function was unchanged. Implants were removed from 10 participants. No analyses were performed to assess how sensitive the results were to changes in the assumptions about the considerable amount of missing data.

Roehrborn et al (2016) reported on 4-year results from patients randomized to PUL in the LIFT study.[35] Of the 140 originally randomized patients, 32 were lost by the 4-year follow-up visit (6 losses were deaths). Of the remaining 108 patients for whom data were available, an additional 29 patients were excluded from analysis for BPH retreatment or protocol deviations. For the 79 (56%) of the 140 subjects included in the analysis, change in IPSS score was -8.8 (precision not given) or -41% (95% CI, -49% to -33%; p<0.001). Significant improvements (vs baseline) were also reported for scores relating to the quality of life, BPH-II, and Qmax. Authors reported that 14% "of the 140 originally enrolled" participants had surgical retreatment at some point during the 4 years; however, the 4-year follow-up included 79 patients, so the denominator for the 14% is not clear, and estimated retreatment rates are likely underestimated since individuals lost to follow-up could also have received retreatment. Attributes of patients who received retreatment were not analyzed. SHIM scores did not differ statistically from baseline.

Roehrborn et al (2017) reported on 5-year results from patients randomized to PUL in the LIFT study.[33] The authors reported 2 analyses. The first was called a per-protocol analysis, which censored patients who had additional BPH procedures, started a BPH medication, or had a protocol deviation. A second analysis was called intention-to-treat analysis, which used last observation carried forward to impute values that were censored in the per-protocol analysis. While there were 104 participants with 5-year data, only 72 patients were included in the per-protocol analysis after exclusion for protocol violations, additional BPH procedures, or treatment with BPH medication. In the intention-to-treat analysis, change in IPSS was -7.85 at 5 years (-35%; 95% CI, -41% to -29%; p<0.001). In the per-protocol analysis, change in IPSS was -7.56 at 5 years (-35.9%; 95% CI, -44% to -27%). Significant improvements, compared with baseline, continued to be reported for scores associated with quality of life, Qmax, and BPH-II.

Subsection Summary - LIFT Study: The LIFT RCT compared PUL with a sham procedure in individuals who had completed a washout period for BPH medications before enrollment. The PUL procedure was associated with greater improvements in lower urinary tract symptoms compared with sham; additionally, the PUL procedure was found to have not worsened sexual function after 3 months of follow-up. After 3 months, patients were given the option to have PUL surgery and about 80% of the sham patients did so. Functional improvements, compared with baseline, appear durable in patients over 2 years and are consistent with the BPH6 study. Follow-up over 3 to 5 years was notable for a high number of patients who were either excluded or lost.

Section Summary: Randomized Controlled Trials
The BPH6 study demonstrated that PUL is noninferior to TURP when assessed by a composite score, which reflects concurrent improvements in validated scales of symptoms, safety, and sexual function. These findings are reflected in the analysis of the individual aspects of the composite score. PUL demonstrates measurable improvements in urinary symptoms to 2 years and is superior to TURP in preserving sexual function. These findings were confirmed in the LIFT study, which compared PUL with a sham treatment. Prior to crossover at 3 months, patients were found to have greater improvement in urinary symptoms and preserved sexual function relative

to patients receiving sham treatment. After 3 months, 80% of patients who had received a sham treatment chose to have the PUL procedure. Patients treated with PUL had improvement of urinary symptoms with preservation of sexual function, consistent with the BPH6 study. These findings were preserved in a subset of patients over 3 to 5 years; a high number of patients were either excluded or lost to follow-up during this time.

SUMMARY OF EVIDENCE

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

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input on prostatic urethral lift for 3 indications was received from 4 respondents, including 2 physician-level responses identified by 1 specialty society and 2 physicians from 1 academic center while this policy was under review in 2017. Based on input on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice:

- Use of prostatic urethral lift in individuals with moderate-to-severe lower urinary tract obstruction symptoms (due to benign prostatic hyperplasia) with normal bladder neck, prostate gland <80 mL, and no median lobe enlargement when either of the following 2 criteria is met:
    - Patient is unable to tolerate or has failed medical management; or
    - Patient is not surgical candidate for transurethral resection of the prostate.

Based on the evidence and independent clinical input, the clinical input does not support whether the following indication provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:

- Use of prostatic urethral lift as first-line therapy in individuals with moderate-to-severe lower urinary tract obstruction symptoms (due to benign prostatic hyperplasia) or when the criteria above are not met.

PRACTICE GUIDELINES AND POSITION STATEMENTS

European Association of Urology

In 2017, the European Association of Urology updated its guidelines on urethral lift implants, giving a grade B recommendation for the use of UroLift in individuals with lower urinary tract symptoms who had prostates less than 70 mL with no middle lobe and were interested in preserving ejaculatory function. It noted that "long term effects have not been evaluated."

National Institute for Health and Care Excellence

In 2014, the National Institute for Health and Care Excellence (NICE) published interventional procedural guidance on urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia.[36] These guidelines state: "Current evidence on the efficacy and safety of insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia is adequate to support the use of this procedure."

In 2015, NICE published a medical technology guidance on use of UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia.[37] The guidelines state: "the UroLift system is effective in relieving symptoms of benign prostatic hyperplasia" and "the UroLift system should be considered as an alternative to current surgical procedures for use in a day-case setting in men with lower urinary tract symptoms of benign prostatic hyperplasia who are aged 50 years and older and who have a prostate of less than 100 ml without an obstructing middle lobe."

American Urological Association

The American Urological Association (2018) published guidelines on the surgical management of LUTS attributed to BPH.[6] The guidelines made the following recommendations and statements regarding PUL.

- "Clinicians should consider PUL [prostatic urethral lift] as an option for patients with LUTS [lower urinary tract symptoms] attributed to BPH [benign prostatic hyperplasia] provided prostate volume <80g and verified absence of an obstructive middle lobe; however, patients should be informed that symptom reduction and flow rate improvement is less significant compared to TURP [transurethral resection of the prostate]."
  - "Moderate Recommendation; Evidence Level: Grade C indicating "Benefits > Risks/Burdens (or vice versa); Net benefit (or net harm) appears moderate. Applies to most patients in most circumstances but better evidence is likely to change confidence"
  - "… the quality of evidence for nonserious harms related to the procedure was rated low, while that for incontinence, need for reoperation, and serious harms related to treatment was rated very low."
  - "… patients selecting PUL should be informed that this is a relatively new intervention for LUTS/BPH with uncertainties in long-term durability, though such uncontrolled data are available."

- "PUL may be offered to eligible patients concerned with erectile and ejaculatory function for the treatment of with LUTS attributed to BPH."
  - "Conditional Recommendation; Evidence Level: Grade C indicating "Risks/Burdens unclear; Alternative strategies may be equally reasonable. Better evidence likely to change confidence"

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov in July 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

52441	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant
52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants

ICD-10 Diagnoses

N40.1	Benign prostatic hyperplasia with lower urinary tract symptoms

REVISIONS

01-01-2017	Policy added to the bcbsks.com web site on 12-01-2016 with an effective date of 01-01-2017.
01-30-2018	Updated Description section.
	In Policy section: ▪ Removed previous policy language, "The prostatic urethral lift procedure is considered experimental / investigational for all indications." ▪ Added new policy language, " A. Use of prostatic urethral lift in individuals with moderate-to-severe lower urinary tract obstruction due to benign prostatic hyperplasia may be considered medically necessary when ALL of the following criteria are met: 1. Patient is not an appropriate candidate for a surgical procedure using general anesthesia, such as transurethral resection of the prostate, due to a chronic medical condition including but not limited to cardiopulmonary disease or chronic anticoagulation therapy; AND 2. Patient has persistent or progressive lower urinary tract symptoms or is unable to tolerate medical therapy (α_1-adrenergic antagonists

	maximally titrated, 5α-reductase inhibitors, or combination medication therapy maximally titrated) over a trial period of no less than 6 months; AND 3. Prostate gland volume is ≤80 mL; AND 4. Prostate anatomy demonstrates normal bladder neck without an obstructive or protruding median lobe; AND 5. Patient does not have urinary retention, urinary tract infection, or recent prostatitis (within past year); AND 6. Patient does not have prostate-specific antigen level ≥3 ng/mL, or has had appropriate testing to exclude diagnosis of prostate cancer; AND 7. Patient does not have a contact dermatitis nickel allergy. B. The prostatic urethral lift procedure in other situations is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 code.
	Updated References section.
11-07-2018	Updated Description section.
	In Policy section: ▪ In Item A, added "in individuals 45 years of age or older" to read, "Use of prostatic urethral lift in individuals with moderate-to-severe lower urinary tract obstruction due to benign prostatic hyperplasia may be considered medically necessary in individuals 45 years of age or older when ALL of the following criteria are met:" ▪ Removed previous Item A 1, "Patient is not an appropriate candidate for a surgical procedure using general anesthesia, such as transurethral resection of the prostate, due to a chronic medical condition including but not limited to cardiopulmonary disease or chronic anticoagulation therapy; AND" ▪ In new Item A 1 (previously Item A 2), added "despite" to read, "The patient has persistent or progressive lower urinary tract symptoms despite medical therapy (α_1-adrenergic antagonists maximally titrated, 5α-reductase inhibitors, or combination medication therapy maximally titrated) over a trial period of no less than 6 months, or is unable to tolerate medical therapy; AND" ▪ Removed previous Item A 4, "Prostate anatomy demonstrates normal bladder neck without an obstructive or protruding median lobe; AND" ▪ In new Item A 3 (previously Item A 5), removed "urinary retention" to read, "Patient does not have urinary tract infection or recent prostatitis (within past year)"
	Updated Rationale section.
	Updated References section.

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