

Technology Assessment



**Technology
Assessment Program**

**Agency for Healthcare
Research and Quality**

540 Gaither Road

Rockville, Maryland 20850

Treatments for Benign Prostatic Hyperplasia

August 2, 2004

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3 **Treatments for Benign Prostatic Hyperplasia**

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16 Prepared for:
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1 **Executive Summary**

2 **Background**

3 Benign prostatic hyperplasia (BPH) is a condition primarily of middle-aged and elderly
4 men. The frequency of the condition increases with age, so it is found in the majority of
5 very elderly men. Consequently, surgical and medical treatments for BPH are some of the
6 most common therapies administered in all of medical practice. BPH is associated with
7 bothersome lower urinary tract symptoms that may include urgency to urinate, frequent
8 urination, weak stream, straining, and/or the sensation of incomplete bladder emptying.
9 These symptoms affect quality of life and sleeping patterns. Medical therapy is available
10 for BPH; however, this may have undesirable side-effects and may provide inadequate
11 relief for more severe cases.

12 Open prostatectomy may be used for men with very large prostates, but has been largely
13 replaced by transurethral resection of the prostate (TURP) as the gold standard for
14 surgical treatment of BPH. Transurethral incision of the prostate (TUIP) is considered by
15 some to be an alternative standard for men with small prostates. Devices and techniques
16 similar to TURP are used for transurethral electrovaporization (TUEVP) and transurethral
17 vaporization with resection of the prostate (TUVRP), and these newer techniques have
18 come to be considered variations on the TURP standard.

19 However, the standard surgeries may be accompanied by undesirable complications of
20 blood loss, transfusion and absorption of irrigation fluids and may result in side-effects
21 such as retrograde ejaculation and incontinence. Therefore, there have been attempts to
22 develop new surgical techniques that use lasers, as well as minimally invasive techniques
23 with heat, microwaves, radiofrequencies, and ultrasound, with the intent of developing
24 techniques that are less invasive than TURP (and thus have fewer complications and side-
25 effects), but provide equivalent symptom relief. It is also desirable that these newer
26 treatments have low retreatment rates. Thus, there are many types of outcomes to
27 examine in comparing these less invasive treatments to TURP. For these less invasive
28 treatments, it may not be a simple question of comparative efficacy with TURP, but
29 rather a question of whether lower complication and side-effect rates are a suitable
30 tradeoff for possibly somewhat less symptom relief and possibly a need for retreatment in
31 the future.

32 The primary purpose of this technology assessment is to review the evidence comparing
33 newer forms of surgery or minimally invasive treatments to TURP (or other standard
34 surgical variations), in terms of efficacy, complications, side effects, and retreatment
35 rates.

36 **Methods**

37 ECRI conducted a systematic review of the controlled trial literature on surgical
38 alternatives to standard surgeries for BPH, as well as minimally invasive treatments.
39 These treatments were compared to either the standard surgeries (TURP, open
40 prostatectomy, TUIP, TUEVP, TUVRP), medical therapy, sham, placebo, or no

1 treatment. We searched 17 electronic databases (including Medline and Embase) for
2 relevant articles. These searches were designed to locate all controlled trials of the
3 treatments of interest published since 1975. Searches were conducted in November 2002,
4 and updated in January and May 2003. We also examined the bibliographies of relevant
5 publications. These searches yielded a total of 1,811 citations. Articles that appeared to
6 report on relevant controlled trials (as judged from their abstracts) were retrieved. These
7 articles were read and selected by a priori standards of relevance and quality. This
8 provided an evidence base of 145 articles reporting on 104 separate studies. Trial
9 information and all results at all time points, including figures, were extracted and
10 compiled in evidence tables (Volume II).

11 From the Evidence Tables, we conducted a systematic, qualitative, best-evidence review,
12 giving greater value to data from studies of larger size, longer followup, and higher
13 quality. While all results were tabled and examined, we emphasized patients' symptoms
14 as measured by standardized indexes such as the International Prostate Symptom Score
15 (IPSS), Madsen Score, and Boyarsky Score. We also placed some importance on the
16 main objective physiological measures of maximum flow rate (Qmax) and post-void
17 residual volume (PVR). The precise relationship of these measures to patient symptoms
18 is incompletely understood. However, we believe these objective measures are of interest
19 because it is possible they will correlate with long-term symptom results, which are
20 scarce in the literature. We considered retreatment rates (typically with TURP) of major
21 importance, because the less invasive treatments are intended to replace, or at least
22 postpone TURP. We examined complication and side-effect rates, and called out any
23 differences in these rates between the less invasive treatments and TURP.

24 **Results and Conclusions**

25 *Specific conclusions:*

- 26 • Standard surgical alternatives to TURP include transurethral electrovaporization
27 techniques (TUEVP and TUVRP), open prostatectomy, and transurethral incision
28 of the prostate (TUIP).
- 29 • Because electrovaporization involves skills and devices similar to those used in
30 TURP, it can be considered a modification of TURP. Symptoms and peak urinary
31 flow rates are similar after TUEVP, TUVRP and TURP. Quality of life is also
32 similar after TUEVP and TURP. Both hospitalization time and catheterization time
33 are shorter for TUEVP.
- 34 • There are no current direct comparisons of open prostatectomy to TURP. Open
35 prostatectomy and TURP are now used on different patient populations. Open
36 prostatectomy remains the preferred option for patients with very large prostates.
- 37 • TUIP is a recommended treatment for men with small prostates. TUIP and TURP
38 provide similar symptom relief. TUIP results in lower retrograde ejaculation rates
39 and shorter operation times, as well as shorter catheterization times and hospital
40 stays than TURP. However, TURP results in higher peak urinary flow rates than
41 TUIP.

- 1 • Contact laser ablation of the prostate (CLAP) and TURP resulted in similar
2 improvements in physiological measures. CLAP and TURP provided similar
3 symptom relief and similar quality of life improvements in most trials, but one
4 double-blinded RCT found these outcomes to be less improved after CLAP than
5 after TURP. CLAP results in less blood loss than TURP.
- 6 • One year after surgery, symptoms and quality of life improvements are similar
7 after visual laser ablation of the prostate (VLAP) and TURP. VLAP requires
8 shorter hospitalizations and longer catheterization times than TURP. Two trials
9 report that major adverse events are less likely after VLAP than after TURP. Three
10 trials report that patients who receive VLAP are more likely to require retreatment
11 than patients who receive TURP.
- 12 • One controlled trial reported that symptoms and physiological measures improve to
13 a similar degree after holmium laser ablation of the prostate (HoLAP) and TURP.
14 This RCT also reported that HoLAP operations take longer than TURP operations.
- 15 • One trial reported that holmium laser resection of the prostate (HoLRP) and TURP
16 improve symptoms to a similar degree and that HoLRP operations take longer than
17 TURP operations, but require shorter lengths of stay and catheterization times than
18 TURP.
- 19 • Two trials reported that after six months, holmium laser enucleation of the prostate
20 (HoLEP) and open prostatectomy yield similar symptom improvement in patients
21 with large prostates. Two trials reported that HoLEP required shorter hospital stays
22 and one trial reported that HoLEP required shorter catheterization times.
- 23 • Interstitial laser coagulation (ILC) and TURP generally provide similar
24 improvements in symptoms and quality of life. Results for physiological measures
25 were mixed. Two trials reported higher retreatment rates after ILC. Unlike TURP,
26 ILC may not require any hospitalization time, but this may be offset by a longer
27 catheterization time.
- 28 • Hybrid laser techniques are too varied to permit general conclusions about this
29 category of treatment for BPH.
- 30 • Radiofrequency needle ablation (RFNA) results in less symptom and physiological
31 improvement than TURP up to 24 months after treatment, and two trials reported
32 that the two treatments have similar effects on quality of life. One trial reported
33 that decreased ejaculate and retrograde ejaculation occur less often after RFNA
34 than after TURP.
- 35 • Only one study examined high frequency ultrasound (HIFU), but it was not
36 randomized, and patients in its groups were not comparable.
- 37 • Cooling transurethral microwave thermotherapy (TUMT) leads to improved
38 symptoms and physiological measures up to 12 months after treatment. Most trials
39 report that cooling TUMT provides less symptom relief and less improvement in
40 physiological measures than does TURP. One trial reported that retrograde
41 ejaculation was less common after TUMT than after TURP. Retreatment rates may
42 be higher after cooling TUMT than after TURP.

- 1 • One RCT reported that non-cooling TUMT may improve symptoms but has
2 associated adverse events. One RCT reported that non-cooling TUMT and TURP
3 yield similar improvements in symptoms and physiological measures, and each has
4 different adverse events.
- 5 • One retrospective study reported that fixed stents provide more symptom relief and
6 greater improvements in peak urinary flow rates than spiral stents, transurethral
7 thermotherapy (TUT) and transrectal hyperthermia (TRH).
- 8 • TRH, TUT, balloon dilation, and transurethral ultrasound-guided laser-induced
9 prostatectomy (TULIP) are outdated technologies not currently recommended by
10 any professional organization.
- 11 • Ethanol ablation, photoselective vaporization of the prostate (PVP) and water-
12 induced thermotherapy (WIT) are emerging therapies not yet studied in controlled
13 trials.

14 ***General conclusions:***

15 The purpose of newer treatments for BPH is to approximate the efficacy of TURP and the
16 other standard surgeries while decreasing the potential harms associated with these
17 surgeries. Some of the less invasive treatments do appear to have fewer and/or less severe
18 immediate complications and side effects, and symptom relief approaches that of TURP.
19 Retreatment rates suggest that symptom relief may not be as long lasting as with TURP.
20 However, the published controlled trials are mostly small and short-term, and few of
21 them completely reported retreatment rates (particularly the need for TURP), adverse
22 events, and harms. Long-term effects of these treatments are currently unknown.

1 Introduction

2 Purpose of Report

3 The aim of this report is to provide CMS with an overview of surgical and minimally
4 invasive procedures for the treatment of benign prostatic hyperplasia (BPH). Medical
5 therapy is not considered in this report, except when it served as a control group.

6 The specific purposes of this report are to:

- 7 • Review the relevant health outcomes for surgical and minimally invasive treatments
8 for benign prostatic hyperplasia (BPH)
- 9 • Review the literature on patient utilities for outcomes of treatments for BPH
- 10 • Describe the surgical and non-surgical options for the treatment of BPH, including a
11 narrative review of technical issues associated with each option, potential adverse
12 effects and training issues
- 13 • Conduct a systematic narrative review of the clinical literature comparing the
14 alternative surgical and less invasive treatment options to transurethral resection of
15 the prostate (TURP), and to each other where possible, with attention to data on
16 beneficial and adverse effects.

17 Background

18 Benign prostatic hyperplasia (BPH) is a condition primarily of middle-aged and elderly
19 men. Frequency of the condition increases with age, and it is found in the majority of
20 very elderly men. Consequently, surgical and medical treatments for BPH are some of the
21 most common therapies administered in all of medical practice.(1,2)

22 BPH is a complicated condition. It can be associated with bothersome lower urinary tract
23 symptoms (LUTS) that affect quality of life and sleeping patterns. LUTS, which may
24 include urgency to urinate, frequent urination, weak stream, straining, and/or the
25 sensation of incomplete bladder emptying, are usually the chief complaints of patients
26 with BPH.(3) In the most severe stage of BPH, the inability to completely empty the
27 bladder may progress to complete urinary blockage, which can in turn lead to kidney
28 damage.(4)

29 LUTS may be also accompanied by bladder outlet obstruction (BOO), and these
30 conditions may be caused by histologically-confirmed BPH, an enlarged prostate gland,
31 or other causes. The Fifth International Consultation on BPH of 2001 (ICBPH)
32 recommended that the general term LUTS be used until there is more knowledge of the
33 causative association of BPH with particular symptoms.(5) However, only a few recent
34 trials have followed this recommendation. Most trials used the term BPH as a general
35 term encompassing all of the above terms, and many of the trial publications did not offer
36 very specific definitions of BPH. Therefore, throughout this document, we use BPH as a
37 general term for all of the above concepts.

1 In recent years, surgical treatment of BPH has been increasingly replaced with medical
2 management, which can improve mild to moderate symptoms and slow the progression
3 toward severe symptoms. However, medication may have undesirable side-effects, and
4 may not provide adequate relief for chronic severe BPH. In such cases, surgery or
5 minimally invasive procedures may be offered.

6 Transurethral resection of the prostate (TURP) is the standard surgical treatment for
7 chronic severe BPH, although open prostatectomy may be required for men with very
8 large prostates.(4) Transurethral electrovaporization of the prostate (TUEVP) is a
9 procedure related to TURP that uses much of the same equipment and skills, and has
10 come to be considered by some a standard variation of TURP. Likewise, transurethral
11 incision of the prostate (TUIP), a less radical procedure that slices through prostate tissue
12 rather than removing it, has also come to be considered by some a surgical standard, but
13 limited to men with small prostates.(6)

14 These standard surgical procedures, however, can result in blood loss requiring
15 transfusion, reaction to irrigation fluids (TURP syndrome),(7-11) incontinence,
16 impotence, cardio-pulmonary events, stroke, and even death.(2,12-16) These procedures
17 also involve regional or general anesthesia, with their inherent potential complications,
18 a hospital stay of 1.5 days or more, as well as catheterization during one or two days of
19 recovery. In recent years, less invasive alternatives have been explored that will minimize
20 or altogether avoid these undesirable results.(17) Therefore, the major purpose of this
21 report is to compare these newer less invasive technologies to TURP and its variants.

22 **Prostate cancer detection**

23 There can occasionally be an overlap of symptoms between prostate cancer and BPH;
24 therefore, prostate cancer is typically investigated in the diagnostic workup of LUTS and
25 BOO. TURP is not a diagnostic test for prostate cancer, but one advantage that it does
26 provide while treating LUTS is that it provides tissue for histological detection of
27 prostate cancer. This leads to early detection of some incidental cases of prostate cancer,
28 as well as some clinically irrelevant cases. With the advent of less invasive devices and
29 procedures for LUTS treatment that do not provide prostate tissue samples, there was
30 concern that some incidental cases of prostate cancer could go undetected. Prostate
31 cancer detection currently relies primarily on prostatic specific antigen (PSA) and
32 transperineal prostate biopsies, which to some extent has allayed such concerns.
33 Nevertheless, pretreatment PSA assays and biopsies may miss some prostate cancers that
34 are detected at TURP.(18)

35 The importance of this prostate cancer detection issue and whether, or to what extent,
36 it should influence the choice of treatment for BPH is unclear. However, the Fifth ICBPH
37 advised that this issue be considered in men with more than ten years' life expectancy
38 when choosing a treatment for BPH.(19) Importantly, such younger men are often
39 considered for less invasive treatments with potentially fewer sexual side effects; and
40 many such procedures retain no tissue for biopsy sampling. Resolution of this prostate
41 cancer diagnostic issue is beyond the scope of this technology assessment, nevertheless,
42 where appropriate, we mention the availability of prostate tissue samples in our
43 descriptions of the various surgeries and less invasive treatments for BPH.

1 **Outcome measures**

2 Several different types of outcome measures are important when evaluating BPH
 3 treatment efficacy, and we discuss each of them when considering each treatment.
 4 Table 1 below outlines these different categories of outcome measures and provides
 5 examples of each.

6 **Table 1. Description of Outcome Measures**

Outcome measure category	Description	Examples
Symptoms	Patient’s subjective experience of having BPH. Obtained using questionnaires completed by patients.	International Prostate Symptom Score (IPSS)(20) Madsen-Iverson Scale(21)
Quality of life	Patient’s ability to perform daily functions and enjoy life, including cognitive abilities, activities of daily living, and family relationships. Questionnaires may relate specifically to BPH or be more generalized.	Short Form 36 (SF-36) BPH Impact Index IPSS QoL Score
Physiological measures	Patient’s physiological status as it relates to BPH, including measures of prostate size and urine flow. Does not reflect patient experience.	Peak flow rate (Qmax) Post-void residual urine volume (PVR) Voided volume
Retreatment rate	Proportion of patients requiring or requesting another treatment after undergoing the treatment in question. Usually calculated a number of weeks or months after treatment.	
Adverse events	Harmful outcomes experienced after treatment, primarily physiological.	TURP Syndrome Retrograde Ejaculation
Perioperative outcomes	Outcomes that occur during or shortly after the treatment.	Procedure time Blood loss Hospitalization time

7

1 Further discussion of these outcome measures, including a discussion of advantages and
2 disadvantages of each, is provided in Appendix A.

3 Patients do not view the outcomes listed in Table 1 as equally important, and different
4 patients may perceive any single outcome differently. For example, one patient might
5 quite negatively perceive having to get up at night to urinate, but another might not be
6 bothered by this symptom. The notion that different patients can have different opinions
7 about the same outcome has sparked interest in *utility assessment* in patients with BPH.
8 Using utilities, a patient can express his opinions about the relative values of different
9 outcomes. The available data on BPH patients' utilities are sparse: only two low-powered
10 studies have reported such data.(22,23) Ackerman et al. (2000)(22) found that patients
11 perceived severe incontinence and urinary retention to be the worst among the assessed
12 long-term outcomes. Schulz et al. (2002)(23) reported that the typical patient was willing
13 to give up 14%-20% of his lifespan in order to relieve his BPH symptoms. Background
14 about utilities, as well as detailed tables of published utility data, appear in Appendix B.

1 **Methods**

2 **Literature Search**

3 To obtain information for this technology assessment, we searched 17 electronic
4 databases (including Medline and Embase) for relevant articles. These searches were
5 specifically designed to locate all controlled trials of treatments for BPH published
6 since 1975. The full list of databases and search strategies is in Appendix C. Searches
7 were conducted in November 2002, and updated in January and May 2003. We also
8 examined the bibliographies of relevant publications. These searches yielded a total of
9 1,811 citations.

10 **Selection Criteria**

11 We read each abstract and applied *a priori* inclusion criteria (Table 2) to determine
12 whether to retrieve the full article. We developed these criteria in consultation with
13 The Agency for Healthcare Research and Quality (AHRQ). If the abstract left doubt
14 about whether the article met the inclusion criteria, it was retrieved and the determination
15 about whether to include it was made from the full text. A total of 344 articles were
16 retrieved from the literature searches and reference lists in other articles. To avoid
17 double-counting of patients, we extracted only unique data from multiple publications of
18 the same trial.

1 **Table 2. Study inclusion criteria**

Category	Inclusion Criteria
Publication date	1975 through December 2002. Treatments for BPH have changed greatly since 1975, and the results of treatments before 1975 are less relevant to patients than more recent treatments.
Publication type	Full articles. The only exception to this was the inclusion of relevant abstracts presented at the May 2003 meeting of the American Urological Association. These abstracts were not included in figures or evidence tables, and our discussion of them is restricted to the text in the relevant section of the report.
Study design	Any controlled trial with at least 10 patients per group. We included controlled trials even if they were nonrandomized, historically controlled, matched controlled, retrospective controlled, or any other type of reasonably-matched comparative design. Single group studies were not included because of the known placebo and regression effects of treatments for BPH (see discussion in the earlier section on descriptions of outcomes).
Participants	Men with symptomatic BPH.
Treatments	Any treatments for men with BPH that have been published in controlled or comparative studies. This includes all of the treatments discussed in this report. The historical surgical standard of TURP was included only if it served as a control for one of the other treatments of interest.
Control treatments	Standard surgeries such as TURP, TUEVP, open prostatectomy and TUIP, as well as placebo, sham surgery, medication, watchful waiting, or no treatment. Studies of the historical standards of watchful waiting and medication were included only if they served as controls for one of the other treatments of interest.
Outcomes	We set no restrictions regarding the reporting of outcomes, because all outcomes were considered relevant.

2

3 **Evidence Base**

4 Applying the study selection criteria yielded 164 articles. We excluded 19 of these
 5 articles for reasons listed in Appendix D. Thus, the evidence base consisted of
 6 145 articles reporting on 104 separate studies.

7 **Data Extraction**

8 Three methodologists extracted information from the included trials. This information
 9 included not only outcome results, but also study location, randomization, whether a trial
 10 was prospective, blinding of patients, blinding of raters, intention-to-treat analysis, and
 11 patient inclusion criteria.

12 Based on the recommendations of AHRQ, we extracted all reported measures at all
 13 reported time points after surgery. This allowed us to identify trends in data, and to

1 empirically determine whether data at earlier time points indexed treatment success as
2 reliably as data gathered at later times. If data were reported in figures but not in text,
3 ECRI estimated them from the figures. When study authors did not report dichotomous
4 data as percentages, ECRI computed percentages. All extracted information, including
5 author errors and reporting discrepancies within and between publications, is noted in the
6 Evidence Tables.

7 Two additional methodologists audited all of the information entered into evidence tables
8 from 51 of the 104 studies (49%). These 51 studies were randomly selected using a SAS
9 random number generator. The error rate was less than 0.5%. These errors were
10 subsequently corrected, so the total error rate, including data entry and typographical
11 errors, in the final evidence tables is less than 0.25%.

12 The evidence tables for all studies and all outcomes are found in Volume II of this report.
13 Definitions of treatment acronyms, as well as definitions of abbreviations that are in the
14 Evidence tables, appear in Appendix E.

15 **Analytic Approach**

16 This report takes the form of a systematic narrative review. Evidence tables (Volume II
17 of this report) provide an essential tool for distilling and organizing the most important
18 information from the published clinical trials. From these tables, ECRI identified the
19 most clinically relevant trials, organized the discussion of the results, and formulated
20 conclusions.

21 Inasmuch as there were many studies of similar quality for some technologies, it was not
22 always possible to select the “best” study for discussion and analysis. Therefore, ECRI
23 considered the results across all relevant controlled studies wherever appropriate, giving
24 greater weight to studies of larger size, longer followup, and higher quality.

25 There is not space herein to provide the numbers and full reasoning behind all of the
26 conclusions, and the reader is directed to the evidence tables on which all of the
27 conclusions were based.

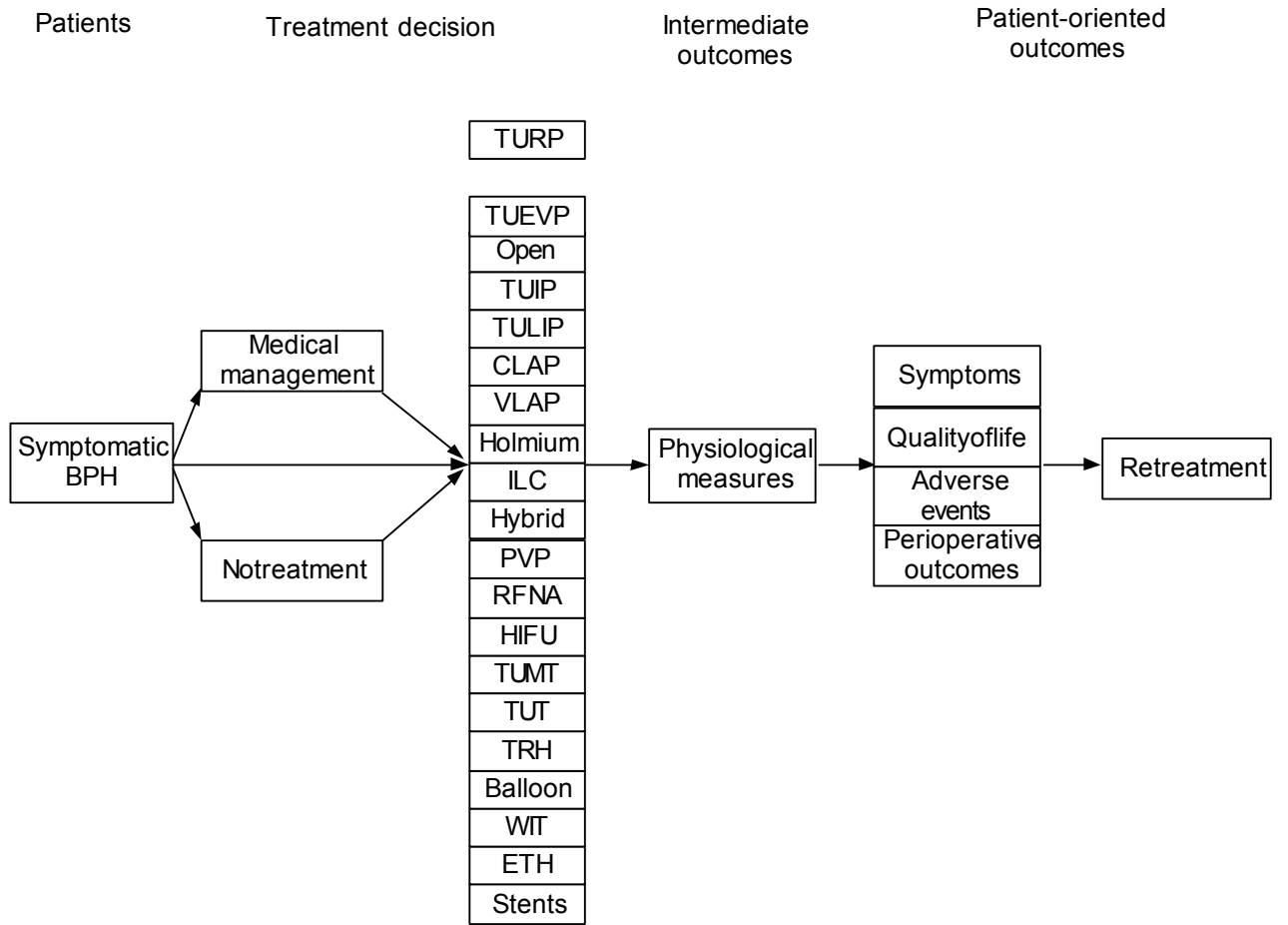
28 Figure 1 shows the analytic framework for this report. Patients with symptomatic BPH
29 may have mild symptoms and thus may receive no treatment or medical management.
30 Patients with moderate or severe symptoms that cannot be controlled through medical
31 management may receive one of the many alternative treatments that are the focus of this
32 report. The choice among these alternatives can be influenced by many factors including
33 prostate size, availability of treatments at the treating institution, expertise of treating
34 physician, and patient preference. TURP is considered the “gold standard” treatment for
35 BPH, but less invasive treatment alternatives may be attempted first to avoid or postpone
36 TURP (as discussed in the Introduction section).

37 Among the outcomes measured after treatment, some are intermediate outcomes
38 (physiological measures of urinary tract function such as peak urinary flow rate), whereas

1 others are patient-oriented (symptoms, quality of life, adverse events, perioperative
2 measures, and retreatment)¹. The patient-oriented outcomes are more important than the
3 intermediate outcomes because they more directly measure what matters to patients.
4 Also, the relationship of the physiological measures to the symptoms is complex and
5 poorly understood. Retreatment is a key outcome because it is a marker for treatment
6 failure, and because a major rationale for the less invasive treatments is to avoid TURP.
7 Alternatives to TURP may be associated with fewer adverse and perioperative events, but
8 patients who receive them may be more likely to require retreatment due to insufficient
9 resolution of symptoms. Therefore, the decision to use a new treatment may involve
10 deciding if the tradeoff between adverse effects and efficacy is acceptable, rather than a
11 simple decision on whether the treatment has equal efficacy with TURP. For each
12 treatment in the Results section, we considered all of the above types of outcomes.

¹ All outcome categories are further described in Table 1 of the Introduction and in Appendix A.

1 **Figure 1. Analytic Framework**



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1 Results

2 Quality of the BPH Literature

3 We considered only controlled trials for this evidence report, because controlled trials
4 provide an essential context for evaluating a new treatment. A properly blinded,
5 randomized controlled trial (RCT) provides an additional benefit of minimizing the
6 effects of extraneous variables, so that results can be attributed solely to the treatment
7 being studied.

8 Use of a control group is particularly important in studies of BPH treatment. This is
9 because men may enter studies when their symptoms are at their worst and, these
10 symptoms will often improve even in the absence of treatment (a phenomenon known as
11 “regression to the mean”). We comment on data demonstrating this phenomenon in the
12 Results section. Sech et al.(24) have also documented the existence of regression to the
13 mean in studies of BPH.

14 Most of the BPH studies included in this review randomly assigned patients to groups.
15 Randomization obviates the need to match groups on patient characteristics and baseline
16 disease severity, although these items are presented in the Evidence Tables. Also
17 included are a few trials that were nonrandomized prospective or retrospective
18 comparisons that appeared to have reasonably well-matched groups of patients. A few
19 trials that assigned treatment on the basis of prostate size or other patient characteristics
20 were considered to have non-comparable treatment groups, and were excluded.

21 Almost no trials reported whether patients were blinded to their treatment, and very few
22 studies reported blinding of outcome raters. Such reporting of blinding was so rare that
23 we did not comment on the lack of blinding with every comparison (although it is
24 tabulated in the evidence tables), but rather pointed out the few trials where blinding was
25 reported. Because of the strong potential for placebo effects in BPH symptom reporting,
26 the lack of reporting of blinding may be a cause of bias in symptom results. That is,
27 patients who knew they received the “new” treatment may have anticipated better results
28 and may have had a substantially stronger placebo effect than patients who knew they
29 received the control or standard treatment. Placebo effects in objective physiological
30 measures such as Qmax are less of a concern.

31 The need for equivalency trials

32 Medical statisticians(25-27) as well as regulatory agencies(28-33) have in recent years
33 recognized that using trials to show that two treatments are equivalent (called
34 “equivalency,” “non-inferiority,” or “active-control” trials) requires a clear *a priori*
35 decision about the size of a clinically meaningful difference, a certain minimum study
36 size, and appropriate statistical analysis (the null hypothesis must be reversed). Yet none
37 of the relevant BPH trials were conducted or analyzed as equivalency trials. Using
38 standard statistical tests designed to detect a “statistically significant difference”
39 (typically with a p-value of 0.05) can be misleading in the absence of calculations

1 demonstrating adequate statistical power. Yet most of the included BPH trials did not
2 demonstrate adequate statistical power.

3 Because of these considerations, many of the studies that compare BPH treatments must
4 be cautiously interpreted. Many of them are low-powered. If a study is too small to detect
5 a clinically meaningful difference, the finding of “no statistically significant difference”
6 can be misinterpreted as implying equivalence.(25,34-37) Further, the less statistical
7 power a trial has, the easier it is to misinterpret its results. Smaller trials have less
8 statistical power to detect clinically important differences with standard statistical
9 significance thresholds (e.g., p-values of less than 0.05). Because of the danger of such
10 misinterpretation, and because none of the BPH trials evaluated in this report were
11 designed and analyzed as equivalency trials by their authors, we emphasize throughout
12 this report that “no statistically significant difference” merely means the trial cannot
13 conclusively demonstrate a difference, and does not imply equivalence. We caution the
14 reader against misinterpretation of such findings.

15 **Confounds of high attrition and retreatment rates**

16 Commonly, there were large discrepancies between the number of patients enrolled or
17 treated and the number of patients in the results for the longest followup time. In most
18 studies this did not appear to result from attrition, but rather because results were
19 published before all patients had reached the longest time point (“right censoring”).
20 While in many studies this caused the results at the longest time to be less reliable,
21 nevertheless, this practice provided valuable information on the much-needed results at
22 the longer time points. In general, the results at these longer time points did not appear to
23 differ from similar time points in studies that waited for complete followup before
24 publishing. Therefore, this large apparent discrepancy in some studies may not be a
25 serious cause of bias.

26 Few, if any, of the included BPH trials were conducted strictly according to intention-to-
27 treat principles. Few reported on patient exclusions that occurred after enrollment and
28 before treatment, and those that did report this had negligibly small numbers of patients
29 removed from trials in this manner. Therefore, this type of violation of intent-to-treat
30 principles appears to be a negligible threat to validity. Patients who received a treatment
31 almost always appeared to be kept with that treatment group for the reporting of results,
32 even if they were subsequently treated with another treatment. Thus, in the important
33 sense of having no crossovers, most of these studies conformed to intention-to-treat (the
34 few exceptions are noted in the text and tables, if the authors provided such information).

35 In studies with high retreatment rates, interpretation of the results is difficult. In the case
36 of dichotomous outcomes such as success/failure, retreatment could simply be counted as
37 a treatment failure. However, there is no uniform definition of treatment failure, and
38 few studies reported this outcome. Furthermore, recalculation and correction of reported
39 results was beyond the scope of this technology assessment. For data that is not
40 dichotomous, but is reported as means of continuous outcomes, there is no simple,
41 reliable method for recalculating to account for high retreatment rates (say over about
42 10%). There are three possible ways authors might handle this difficulty, and they all
43 may lead to an overestimation of the efficacy of an intervention with a high retreatment

1 rate. If the authors excluded the retreated patients, then the remaining patients were the
2 patients with the best response to treatment. If the retreated patients were included as part
3 of the analysis of results of the initial treatment, then the results not only reflect the
4 efficacy of that treatment, but also the retreatment method, possibly inflating estimates of
5 efficacy. If the authors crossed over the retreated cases to the arm for the retreatment
6 method, that would be a violation of intention-to-treat principles and a threat to the
7 original randomization. Because of these problems, retreatment rates were important to
8 consider in arriving at our conclusions, and we treated with caution those trials that
9 reported a high retreatment rate. In such trials, the retreatment rate itself might be the
10 most important and only interpretable outcome.

11 **Adverse events**

12 In the present literature, treatment-related adverse events are incompletely reported, or
13 are reported using different terminology and definitions. Further, many studies were
14 too small to detect adverse events or to provide reliable rates of occurrence. If the authors
15 did not report an adverse event, one cannot determine whether the event did not occur or
16 if it was simply not reported. These difficulties prevented a quantitative evaluation of
17 adverse events in this report. In the evidence tables, we included all reported adverse
18 events as described by authors, and considered them in assessing results.

19 **FDA Product Labeling**

20 In evaluating the literature, it is important to determine if a given trial is applying the
21 treatment to the population that was studied when the device received FDA marketing
22 approval or clearance. Treatments may not be as effective for patients for whom the
23 device or treatment was not designed. For example, treating patients with large prostates
24 with certain laser or other heat-based treatments may not be as effective as with patients
25 with smaller prostates for whom the treatment was intended.

26 Where appropriate, we mention FDA clearance indications and contraindications in the
27 text. Full product labeling indications and contraindications for devices are provided in
28 Appendix F. Such information was not available for all devices because many devices
29 cleared under 510k regulations are cleared for general uses (such as many of the lasers).

30 **Standard Surgical Treatments**

31 **Transurethral resection of the prostate (TURP)**

32 *Technology Description and Clinical Issues*

33 TURP is considered the current standard of care for surgical treatment of BPH in most
34 patients and has been the primary choice of treatment for the past 50 years.(3,6,19,38,39)
35 TURP is an endoscopic procedure that requires general or spinal anesthesia and takes
36 30 to 60 minutes to perform. In TURP, the surgeon inserts a resectoscope, a 12-inch long,
37 ½ inch diameter scope that contains a light, irrigating fluid valves, and a wire-loop
38 electrode (approximately 0.3 millimeter in diameter) for cutting and coagulating.
39 An electrosurgical generator is used to power the electrode, usually to 120 W or 150 W.
40 The surgeon uses the wire-loop electrode to remove tissue that is obstructing or pressing

1 against the urethra. Prostatic tissue is generally removed until the capsule is reached.
2 Irrigating fluid maintains the surgeon’s visibility and carries the resected pieces of tissue
3 (chips) into the bladder, which is then flushed out at the end of the TURP procedure.
4 Higher electrosurgical frequencies may be used for coagulation during TURP. Recently,
5 European urologists introduced a high-frequency technique called “coagulating
6 intermittent cutting” that is intended to reduce perioperative blood loss in patients at
7 increased risk for bleeding.(40)

8 Until recently, TURP procedures were performed using monopolar electrosurgery, in
9 which an active electrode is located in the surgical handpiece, and a dispersive (return)
10 electrode is placed on the patient (usually on the outer thigh or lower abdomen). The
11 dispersive electrode, also called a grounding pad, directs electrical current flow from the
12 patient back to the power unit and reduces current density as energy flows from the
13 patient, thereby minimizing the possibility of burns at the return electrode. In bipolar
14 TURP, much of the instrumentation and surgical technique are the same as for monopolar
15 TURP. A dedicated bipolar electrosurgical generator may be used, but some general
16 electrosurgical devices can be used for both modes. Also, both modes can be used in the
17 same procedure, for example, for cutting and coagulating. Dual wire-loop electrodes are
18 used, in which the active and return electrodes are located in one handpiece, and the
19 electrosurgical current flows between the electrodes through conducting saline, rather
20 than from the active wire-loop electrode, through the patient to the grounding pad
21 (dispersive electrode) as in monopolar TURP. Therefore, the dispersive electrode pad
22 placed on the patient is not required in bipolar TURP. Because of the differences in
23 energy delivery, bipolar TURP can result in less granulation tissue and less tissue
24 charring than monopolar TURP. However, bipolar TURP requires slower movement of
25 the wire-loop electrodes. Bipolar electrodes require less power than monopolar
26 electrodes, because there is less tissue between the electrodes to create impedance.(41)

27 Monopolar TURP requires the use of a nonconducting irrigation fluid. Sterile water was
28 used up until the 1940s, when it was abandoned because of problems with hemolysis.(42)
29 The current standard irrigant is 1.5% glycine, although mannitol and sorbitol have also
30 been used.(42) Absorption of excess irrigation fluid into the blood stream can cause
31 TURP syndrome, which can include hyponatremia, nausea, temporary blindness,
32 unconsciousness, and rarely death.(7) Bipolar TURP requires saline for current
33 conduction between the two electrodes. This has the potential to eliminate TURP
34 syndrome. However, the use of saline in the narrow urethra introduces the potential for
35 inadvertent damage to non-targeted tissue.

36 Our searches identified no controlled studies directly comparing mono- and bipolar
37 techniques. Only one of the trials included in the present analysis reported which method
38 was used (monopolar),(43) possibly because both methods are considered versions of the
39 standard TURP procedure. Therefore, there is insufficient evidence to draw conclusions
40 about the comparative effects of these two techniques on patient outcomes.(8-11)

41 It is considered undesirable to have a TURP procedure last longer than 60 minutes,
42 because of potential blood loss and irrigation fluid absorption. This has the practical

1 effect of preventing the use of TURP for patients with very large prostates beyond the 70
2 to 100 grams range,(19,44) and such patients may require open prostatectomy.

3 TURP requires catheterization for 24 to 48 hours, and a hospital stay ranging from one to
4 five days. In addition, for at least four weeks after TURP, patients may have restricted
5 physical activity.

6 In a recent landmark study by Borboroglu and colleagues of 520 consecutive TURP
7 patients from 1991-1998,(45) the rate of intraoperative complications was 2.5%,
8 immediate postoperative 10.8%, and late complications 8.5%. The transfusion rate was
9 0.4%. There were no mortalities, meaning the rate was less than 0.2% (1/520). The rate of
10 repeat TURP was 2.5%, with mean followup of 42 months (range: 6 to 84 mos.). These
11 authors found great improvements in all the above rates compared to compilations from
12 previous eras that have often been used by proponents of new treatments in retrospective
13 comparisons to historical controls. In the first year of the Borboroglu study (1991), the
14 catheterization time was 3.5 days and hospital stay 3.8 days, but these were reduced to
15 1.8 and 1.1 days, respectively, for the last year of the study (1998). These large
16 improvements in results over time suggest that even the rates cited in this most recent
17 study may overestimate the TURP complication rates observed in current practice. This
18 indicates the unreliability of comparing uncontrolled study results to historical data.
19 Thus, we base our report mostly on controlled studies in which new treatments were
20 compared directly to a concurrent TURP group.

21 In 21 controlled trials included in the present report with TURP groups with followup of
22 at least 12 months, the retreatment rate in the TURP groups ranged from 0% (0/35)(43) to
23 30% (13/43)².(46) However, the definitions of “retreatment” in these trials were not
24 consistent. Trials with smaller retreatment rates appeared to refer only to TURP
25 retreatment for LUTS, whereas, trials with larger rates appeared to refer to any urological
26 surgical intervention for any reason during followup. Because of the lack of a consistent
27 definition, as well as other between-study differences, across-studies comparisons of
28 retreatment rates are inappropriate in this body of evidence, and the reader is advised to
29 consider only the within-studies comparisons of retreatment rates. Because of the small
30 size of many of the studies and the low frequency of retreatment, even the within-studies
31 retreatment rate comparisons may not be reliable.

32 TURP is performed with general surgical devices such as electrosurgical units, electrodes
33 and endoscopes. These devices are cleared for marketing in the United States through the
34 Food and Drug Administration’s 510(k) premarket notification process.(47)

35 *Clinical Practice Guidelines*

36 In 2000-2001, the Fifth International Consultation on BPH (ICBPH), sponsored by the
37 World Health Organization (WHO) and the Union Internationale Contre le Cancer
38 (UICC), established recommendations for the diagnosis and treatment of BPH, lower

² Adverse event and reoperation rates are always provided with raw numbers as well in this document, unless the authors did not report the number of patients that the statistic was based on.

1 urinary tract symptoms, and bladder outlet obstruction.(48) Recommendations were
2 based on a literature review and opinion of international clinical experts. The Fifth
3 ICBPH considers TURP the “gold standard of interventional therapy” for BPH,(5,19)
4 but suggests that, because morbidity, mortality, and blood transfusion rates are directly
5 related to resection time, TURP should only be performed if the resection can be
6 completed in one hour.(19) The European Association of Urology (EAU) recommends
7 surgical management using TURP, TUIP, or open prostatectomy as a first-line treatment
8 for patients with bothersome BPH symptoms refractory to medical treatment.(49) The
9 AUA also considers TURP to be “the gold standard” for BPH treatment.(3)

10 As TURP is the current standard of care, it is outside the scope of this report to provide a
11 detailed analysis of its efficacy. The above comments are provided as background
12 information.

13 **Transurethral electrovaporization procedures**

14 *Technology Description and Clinical Issues*

15 Transurethral electrovaporization of the prostate (TUEVP, TUVAP, or TUEVAP; also
16 called transurethral vaporization, TUVAP or TVP, or transurethral evaporation, TUEP) has
17 developed since the early 1990s as a variation of TURP. TUEVP and TURP are similarly
18 performed in that both use a standard resectoscope inserted transurethraly, and an
19 electrosurgical unit to deliver energy to an electrode. Thus, TUEVP is considered a
20 modification of TURP.(19,50-52)

21 Electroevaporization procedures differ from TURP and each other according to the type of
22 electrode used and the magnitude of electrical energy applied, both of which determine
23 whether tissue is incised, vaporized, resected into pieces or “chips”, or coagulated. In
24 general, the electrodes used in vaporization procedures are shaped and sized to allow
25 more tissue contact than the standard thin wire loop electrode used for resecting. Prostatic
26 tissue is vaporized using a grooved or spiked rollerball or thicker band-loop electrode.
27 Wire loop electrodes used for electrovaporization are approximately one millimeter in
28 diameter. Due to the high energy and simultaneous vaporization/coagulation of prostate
29 tissue, TUEVP procedures can produce less bleeding than TURP.(19,53,54) After the
30 electrode is inserted through the resectoscope to the area to be treated, an electrical
31 current of 230 to 300 W is applied to heat the obstructing prostate tissue until it turns to
32 steam. A constant flow of irrigating fluid is applied to the heated area to dissipate heat.
33 According to clinicians, TUEVP is difficult to perform in prostates larger than about
34 50 grams, because of the longer operative times required.(55)

35 “Sandwich techniques” have been developed that use the rollerball electrode to vaporize
36 and coagulate first, followed by the standard TURP wire-loop electrode to resect
37 coagulated tissue, and then the rollerball electrode again to complete dissection and
38 coagulation of deeper tissue. In this report, we refer to any technique combining
39 vaporization and resection as transurethral vaporization with resection of the prostate
40 (TUVRP). The “sandwich technique” allows tissue to be removed for pathologic
41 analysis.(53) In addition to the sandwich technique, TUVRP can also be performed with
42 a single thicker loop or band electrode. This enables more contact with prostate tissue

1 than the TURP thin wire-loop electrode, to simultaneously vaporize, cut, and coagulate,
2 without alternating the electrode used. For cutting, energy of 230 to 300 W is used, and
3 for coagulation, energy of 50 to 80 W is used. Regardless of the power setting, the actual
4 power delivered depends on the impedance of the tissue. Too low power can result in less
5 efficient cutting and excess coagulation necrosis, which is considered a cause of
6 persistent postoperative irritative symptoms.(53) Some power generators have the ability
7 to increase current with changing tissue impedance. With TUVRP, resection of tissue
8 “chips” is possible, although cutting times are longer than with TURP because of the time
9 required for vaporization and coagulation. In 2002, a bipolar electrosurgical generator for
10 plasma vaporization and resection was introduced and is being studied in comparison to
11 TURP and TUVRP.

12 Electro vaporization procedures can be performed on an outpatient basis or with an
13 overnight hospital stay. Depending on the patient, general or regional anesthesia, and/or
14 intravenous sedation with local intraurethral analgesic are used. Theoretically,
15 vaporization causes less bleeding because the treated tissue is coagulated and sealed by
16 the higher applied energy and the electrode design (the evidence for this is addressed
17 below). TUEVP and TUVRP are considered easy to teach and learn, because of the
18 similarity to TURP in equipment and technique, and the better visibility due to less
19 bleeding.(52)

20 In our analysis comparing TUEVP with TURP, we considered all TUEVP procedures as
21 a group and did not separate results based on the many different electrode designs. This is
22 in accordance with the way the procedure is commonly categorized by clinicians in the
23 literature. We considered TUVRP to be a separate technique and analyzed these trials
24 separately.(55)

25 TUEVP and TUVRP are performed with general surgical devices such as electrosurgical
26 units, electrodes and endoscopes. There are many electrodes with different shapes for
27 TURP, TUEVP and TUVRP. The electrodes used in the included trials in the present
28 report are listed in the evidence tables that accompany this report. These devices are
29 cleared for marketing in the United States through the Food and Drug Administration’s
30 510(k) premarket notification process.(47)

31 *Clinical Practice Guidelines*

32 The Fifth ICBPH views TUEVP as a variation of the standard TURP procedure that
33 results in less bleeding, and has considered TUVRP an “acceptable” BPH treatment since
34 1997.(19) The AUA concluded(56) that TUEVP shows equivalent short-term symptom
35 improvement to TURP, but has higher rates of postoperative irritative urinary side
36 effects. The AUA states that long-term comparative trials are needed to compare
37 transurethral vaporization to standard TURP. In addition, the AUA considers the newer
38 bipolar plasma vaporization technique an emerging therapy requiring additional data
39 before it can be recommended as a treatment option. The procedure can be offered to
40 appropriate patients, provided outcomes relative to recommended treatments are
41 discussed with the patient.(3)

1 *Findings*

- 2 • **Symptoms and peak urinary flow rates are similar after TUEVP, TUVRP and**
3 **TURP. Quality of life is also similar after TUEVP and TURP. Both**
4 **hospitalization time and catheterization time are shorter for TUEVP.**

5 Seventeen controlled trials compared TUEVP or TUVRP with TURP (N ≥1,100), all but
6 one of which were randomized.(44,50-52,55,57-70) Most studies that reported size
7 criteria excluded patients if their prostates were over 60 or 70 grams. Most trials had data
8 at one year, one trial at two years and one at three years. Thirteen trials evaluated
9 TUEVP, while four trials used a combination of cutting and vaporization
10 (TUVRP).(55,57,58,66)

11 **TUEVP**

12 Twelve trials on TUEVP reported symptom severity. In general, after TUEVP and
13 TURP, patients' symptoms improved from severe to mild, and patients' IPSS scores were
14 similar. TUEVP and TURP also provided similar peak urinary flow rates (Qmax;
15 reported by 15 trials). Five(50,57,60,61,63,71) of the 13 trials on TUEVP reported quality
16 of life (QoL) data, and, again, similar results were observed after the two treatments.

17 The number of patients with retention, stricture, incontinence or retrograde ejaculation
18 was similar after TURP and TUEVP. Five studies reported on post-operative irritative
19 symptoms (caused by sloughing of necrotic tissue). Four of these trials reported more
20 such symptoms with TUEVP than with TURP.(50,60,67,69) However, in one trial, the
21 rates were similar.(61)

22 Two trials reported retreatment rates.(63,68) These rates tended to be lower after TURP
23 but rates were so low for both groups that reliable comparisons cannot be made.

24 Results for operation time were mixed: operation time was shorter for TUEVP in two
25 trials,(51,65) shorter for TURP in two(50,61,70) and the same in two.(60,67)
26 Catheterization time was shorter for TUEVP in seven of eight trials
27 reporting.(50,51,61,65,67,68,70) Hospital stay was shorter for TUEVP in four of five
28 trials reporting this result.(50,61,68,70)

29 **TUVRP**

30 Four trials evaluated TUVRP(55,57,58,66) and found that results were similar for
31 TUVRP and TURP for symptoms and physiological outcomes. Across trials TUVRP and
32 TUEVP showed similar results for symptoms and physiological outcomes, although there
33 was no such direct comparison in any trial.

34 Operation time was longer for TUVRP in two trials(55,58) and the same in two.(57,66)
35 Catheter time was shorter for TUVRP in one trial (48 hrs, vs 96 hrs,)(58) and the same in
36 one (3.4 and 3.3 days).(66) Hospital stay was shorter for TUVRP in the only trial
37 reporting this result (2.5 days vs 4.5 days).(58)

1 **Open prostatectomy**

2 *Technology Description and Clinical Issues*

3 Open prostatectomy is a major surgical procedure in which the obstructing prostate tissue
4 is removed through a lower abdominal incision using a suprapubic (through the bladder)
5 or retropubic (through the prostate capsule) approach. The obstructing tissue is excised in
6 one piece, and the prostate capsule is not removed. (In radical prostatectomy, a treatment
7 for prostate cancer, the entire prostate and capsule are removed.) Open prostatectomy
8 requires general or spinal anesthesia, a three- to five-day hospital stay, and a longer
9 period of catheterization and recovery than TURP. Open prostatectomy is one of the only
10 treatment options for patients with prostate glands greater than 75 to 100 grams,(19,44)
11 and is also performed in patients with other conditions, such as bladder stones, that
12 require an open procedure.(19,49) Therefore, today TURP and open prostatectomy are
13 considered for different populations of patients, and are not considered to directly
14 compete with each other.

15 In the past, although TURP may have been no better than open prostatectomy in terms of
16 symptom improvements and not quite as efficacious in terms of physiological measures,
17 these differences were considered to be outweighed by the shorter operation times and
18 less blood loss. This accounts for TURP’s historical replacement of open prostatectomy
19 as the “gold standard” surgical treatment for BPH, except for men with very large
20 prostates beyond the 70 to 100 grams range.

21 As a surgical procedure, open prostatectomy is not regulated by the FDA.

22 *Clinical Guidelines*

23 The Fifth ICBPH considers that open prostatectomy is “acceptable,” and that it is
24 necessary for patients with prostates larger than 80 to 100 grams. The EAU recommends
25 surgical management using TURP, TUIP, or open prostatectomy as a first-line treatment
26 for patients with bothersome BPH symptoms refractory to medical treatment.(49)

27 *Findings*

- 28 • **There are no current direct comparisons of open prostatectomy to TURP.**
29 **Open prostatectomy and TURP are now used on different patient populations.**

30 There has been only one controlled trial comparing open prostatectomy with TURP,
31 a randomized study by Meyhoff (N = 75) in the 1970s.(46,72) The efficacy and
32 complications for these procedures at that time are likely not relevant to current practices;
33 TURP and open prostatectomy are now considered to have different indications and
34 patient populations.(19)

35 **Transurethral incision of the prostate (TUIP)**

36 *Technology Description and Clinical Issues*

37 TUIP is a surgery that is less invasive than TURP and is usually limited to small prostate
38 glands. In TUIP, the surgeon makes one or two lengthwise internal incisions in the
39 prostate near the bladder, which opens the bladder neck and prostate to reduce pressure

1 on the urethra. Either a laser system or electrical current delivered via an electrosurgical
2 unit can be used to make the incisions (only electrosurgical incisions are considered in
3 this section; laser surgeries are considered in other sections). Because TUIP is less
4 invasive than TURP, it can be performed on an outpatient basis under regional or general
5 anesthesia, although a one- to three-day hospital stay may be required. Although the
6 incision itself does not provide prostate tissue for histological detection of prostate
7 cancer, a biopsy can be taken through the resectoscope at the time of the procedure.(73)

8 TUIP is performed with general surgical devices such as electrosurgical units, electrodes
9 and endoscopes. These devices are cleared for marketing in the United States through the
10 Food and Drug Administration's 510(k) premarket notification process.(47) They are not
11 generally cleared for specific indications.

12 *Clinical Practice Guidelines*

13 TUIP is performed on patients with small prostate glands. The World Health
14 Organization recommends restricting the use of TUIP to patients with prostates 30 grams
15 or less in size.(6) The European Association of Urology (EAU) recommends TUIP for
16 patients with a small prostate gland, no median lobe, and a low risk of associated prostate
17 cancer.(49) The Fifth ICBPH suggested that TUIP can be used to treat prostates
18 up to 80-100 grams in size, but is particularly suited for treating prostates of
19 less than 30 grams.(19) The EAU recommends surgical management using TURP, TUIP,
20 or open prostatectomy as a first-line treatment for patients with bothersome BPH
21 symptoms refractory to medical treatment.(49)

22 *Findings*

- 23 • **TUIP is intended for men with small prostates. TUIP and TURP provide similar**
24 **symptom relief. TUIP results in lower retrograde ejaculation rates and shorter**
25 **operation times, as well as shorter catheterization times and hospital stays than**
26 **TURP. However, TURP results in higher peak urinary flow rates than TUIP.**

27 We identified 10 randomized trials (N = 811) comparing TUIP to TURP.(73-85) Most of
28 these trials followed the majority of patients for two to three years. These trials included
29 only men with prostates smaller than 20 to 40 grams. In these trials, the symptom relief
30 for the two treatments appears similar, but peak urinary flow rate (Qmax) was higher
31 after TURP. None of the studies reported data on quality of life.

32 After TUIP, operation time, days in hospital, and catheterization time were shorter or
33 similar to TURP, and a lower or a similar percentage of patients required transfusions.
34 While most adverse events were similar, the retrograde ejaculation rate was lower after
35 TUIP.

36 Retreatment rates were reported in four trials.(74,76,77,80) In three of the four trials,
37 retreatment rates appear higher for TUIP than for TURP. One study of 85 patients
38 (Jahson 1998) reported that this difference was statistically significant (23% versus
39 5% retreatment rates),(76) while two reported no statistical tests and one reported no
40 statistically significant differences (exact rates not available). However, because the
41 number of patients enrolled in each of these trials was either not reported or was often

1 small (<35 patients per group) and the number of patients requiring retreatment was also
2 low (typically <10), comparison of rates may not be reliable.

3 The 5-year trial by Jahnsen et al. (1998)(76) carried out cystoscopy at 2 years and found
4 adhesions, closed incisions or obstructing lobes in 90% (19/21) of the TUIP patients
5 compared to 39% (9/23) of the TURP patients (statistically significant). A comparable
6 difference was observed at five years. These authors concluded that these findings
7 explained why Qmax is lower and the retreatment rate is higher for TUIP.

8 **Laser Surgical Treatments**

9 **Transurethral ultrasound-guided laser-induced prostatectomy (TULIP)**

10 *Technology Description and Clinical Issues*

11 TULIP was introduced in 1990 and was one of the first laser procedures used for BPH.
12 TULIP is performed with a right-angle-firing Nd:YAG laser probe housed between two
13 ultrasound transducers that are used for real-time sector scanning to position the laser
14 while it is being fired. The laser is fired while the device is moved and rotated through
15 the urethra from the bladder neck to the verumontanum. Coagulation necrosis of the
16 prostate tissue produces shrinking over several weeks following the procedure.

17 TULIP has been replaced by other laser types and techniques (discussed in subsequent
18 sections) that have fewer side effects, shorter postoperative catheterization times, and
19 fewer urinary symptoms. The most recent controlled trial of TULIP was a retrospective
20 review published in 1998 by Japanese researchers, and the patients had likely received
21 the procedure several years before then.(86)

22 *Clinical Practice Guidelines*

23 TULIP is not mentioned in any of the evidence-based BPH guidelines that we identified.

24 *Findings*

25 Because this treatment appears to be outdated, we do not further consider the results of
26 controlled trials on it.

27 **Contact laser ablation of the prostate (CLAP)**

28 *Technology Description and Clinical Issues*

29 Surgeons developed CLAP in the early 1990s in an attempt to avoid the intraoperative
30 complications of TURP, such as blood loss. To perform CLAP, the surgeon places the tip
31 of an Nd:YAG laser in direct contact with the prostatic tissue, which vaporizes it. The
32 laser tip is slowly dragged to create “furrows” across the prostate, thereby reducing
33 prostatic obstruction of the urethra. While the primary mechanism of action in CLAP is
34 vaporization, some tissue coagulation also occurs. As a result, patients require
35 postoperative catheterization to permit sloughing of any coagulated tissue. Unlike TURP,
36 CLAP does not yield samples that can be tested for prostate cancer. CLAP requires
37 extensive training and experience, and some have suggested that a surgeon’s first set of
38 cases be restricted to patients with smaller prostates because they are easier to treat.

1 Results from one RCT suggested that some surgeons experienced difficulty in performing
2 CLAP in patients with prostates of 40-50 grams.(87) We identified a single laser FDA
3 cleared specifically for use during the CLAP procedure: Surgical Laser Technologies'
4 SLT CL MD (Nd:YAG) Contact Laser System and delivery fibers.(88) This laser is
5 cleared only for prostates up to 45 grams.

6 *Clinical Practice Guidelines*

7 The AUA 2003 Guidelines(3) classify CLAP as a surgical approach to BPH and states
8 that the choice of surgical approach is a technical decision based on patient's prostate
9 size, surgeon judgment, and patient's comorbidities. The AUA also states that, while
10 CLAP results in short-term improvements (symptom scores, urinary flow rate) equivalent
11 to TURP, reported rates of postoperative urinary retention and unplanned secondary
12 catheterization are higher following CLAP.

13 The Fifth ICBPH(19) recommends holmium laser treatment and ILC over CLAP due to
14 CLAP's higher treatment failure rates and complications. The EAU(49) does not discuss
15 CLAP in its review of laser therapy, but recommends that side-firing VLAP and ILC be
16 used only for patients on anticoagulants, for patients not eligible for TURP, or for
17 patients with a desire to maintain ejaculation.

18 *Findings*

19 All five of the trials comparing CLAP to TURP used sapphire-tipped laser probes and
20 fibers (MTRL 10) manufactured by Surgical Laser Technologies (Oaks, PA, USA).
21 Four of the five trials used an Nd:YAG laser generator manufactured by the same
22 company,(71,89-91) and the fifth trial used an unspecified Nd:YAG laser generator.(89)
23 There were no controlled trials comparing CLAP devices. However, the similarities
24 among the CLAP devices in these five trials support the grouping of their results.

- 25 • **CLAP and TURP resulted in similar improvements in physiological measures.**
26 **CLAP and TURP provided similar symptom relief and similar quality of life**
27 **improvements in most trials, but one double-blinded RCT found these outcomes**
28 **to be less improved after CLAP than after TURP. CLAP results in less blood**
29 **loss than TURP.**

30 Five controlled trials (N = 346) compared CLAP to TURP.(71,87,89-95) These trials
31 were all randomized, and one was a double-blinded trial that followed patients for three
32 years (the Oxford Laser Prostate trial).(87,91-94) In that trial, symptoms were worse
33 at three years for patients who received CLAP than for those who received
34 TURP(statistically significant). The other four trials found that symptom scores after
35 CLAP and TURP were similar. All five trials found that physiological measures such as
36 Qmax were similar for CLAP and TURP after treatment.

37 The Oxford trial found that one year after treatment, BPH-specific quality of life was
38 slightly worse after CLAP than after TURP (statistically significant). However, quality of
39 life using other measures in other trials was similar after the two treatments.

1 Two trials reported retreatment rates.(87,89,91,94) Keoghane et al. (2000) reported that
 2 patients who received CLAP were more likely to require retreatment by three year
 3 followup than those who received TURP (18% vs 9%) (statistical significance not
 4 reported). The authors suggest that this difference may have been caused by surgeons'
 5 limited experience with CLAP.(91) Another possible explanation is the inclusion of
 6 patients with large prostates, who are more difficult to treat and may be less appropriate
 7 for CLAP. Three of the five trials(89,90,95) either excluded patients with large prostates
 8 (e.g., >40 grams) or required surgeons to have performed a minimum of 20 previous
 9 CLAP procedures.(90) One of these three trials (Tuhkanen et al., 1999)(89) reported that
 10 no patients in either group required retreatment, suggesting that it enrolled too few
 11 patients to reliably determine retreatment rates.

12 Operation times for CLAP and TURP were generally similar (30-40 minutes), but two
 13 trials reported that during CLAP, patients lost significantly less blood (37-59 mL versus
 14 175-200 mL during TURP).(89,91)

15 Three of the five trials reported comparative data on adverse events. One trial (N = 32)
 16 found a statistically significantly lower rate of retrograde ejaculation after CLAP than
 17 after TURP (6% versus 81%).(89) None of the other trials reported retrograde ejaculation
 18 rates. No other statistically significant differences in adverse event rates were reported,
 19 but it is possible that the trials enrolled too few patients to detect such differences.

20 **Visual laser ablation of the prostate (VLAP)**

21 *Technology Description and Clinical Issues*

22 In VLAP,³ the Nd:YAG laser is held a short distance (2 mm) from the prostate tissue
 23 (unlike CLAP in which there is direct tissue contact, see previous section). The primary
 24 mechanism of tissue destruction is coagulation rather than vaporization, and the
 25 coagulated tissue sloughs away over the next several weeks. Therefore, VLAP requires
 26 longer postprocedural catheterization times ranging from five days to several weeks, and
 27 may require recatheterization. During the sloughing period, patients may also experience
 28 infection, swelling, and pain during urination. Several variations of VLAP have been
 29 developed that use different types of lasers, laser fibers, wattages, and application
 30 techniques. Unlike TURP, VLAP does not yield samples that can be tested for prostate
 31 cancer.

32 VLAP is typically reserved for patients with small or moderately-sized prostates
 33 (<80 grams), because patients with larger prostates would require multiple sessions.
 34 Patients with chronic urinary tract infection or bacterial prostatitis are not good
 35 candidates because coagulated tissue may become infected.(19) VLAP may be
 36 particularly appropriate for patients who are on anticoagulants because the laser seals
 37 blood vessels.

38 VLAP devices that have received FDA 510(k) clearance to be marketed in the treatment
 39 of BPH include Trimedyn's Optilase Nd:YAG Laser System Models 1000, 4000, and

³ VLAP is also referred to as non-contact laser ablation of the prostate or laser coagulation of the prostate.

1 1000-100 (PL100) used with Trimedynе’s UroGold or UroMax Right Angle Laser
2 Fibers, and Laserscope’s 800 Series and Orion Series KTP/Nd:YAG Surgical Laser
3 Systems used with the Angled Delivery Devices (ADD Family Product Line). The
4 Trimedynе system is indicated for coagulation of soft tissue for prostatectomy in the
5 treatment of BPH. The FDA clearance did not mention whether the device was indicated
6 for patients with specific prostate sizes. The Laserscope system is indicated for men
7 50 years and older with prostatic volumes of 60 cc or less.

8 *Clinical Practice Guidelines*

9 The AUA Guidelines(3) classify VLAP as a surgical approach to BPH and states that the
10 choice of surgical approach is a technical decision based on patient’s prostate size,
11 surgeon judgment, and patient’s comorbidities. AUA also states that, while VLAP results
12 in short-term improvements (symptom scores, urinary flow rate) equivalent to TURP,
13 reported rates of postoperative irritative voiding and unplanned and prolonged
14 postoperative catheterization are higher following VLAP.

15 The Fifth ICBPH(19) classifies VLAP as an “acceptable” treatment, but recommends
16 holmium laser treatment and ILC over VLAP due to higher retreatment rates and
17 complications. The EAU guideline(49) does not recommend VLAP as a first-line
18 therapy, but advises that VLAP be used only for patients on anticoagulants, for patients
19 not eligible for TURP, or for patients with a desire to maintain ejaculation.

20 *Findings*

21 Ten trials compared VLAP to TURP. Eight of these trials(95-102) used the Urolase fiber
22 (Bard, Covington, GA, USA), one(103) used the Ultraline fiber (Lasersonics, Tokyo,
23 Japan), and one(63) used the ADD fiber (Laserscope, San Jose, CA, USA). No controlled
24 trials of VLAP have compared these fibers, thus one cannot determine from direct
25 evidence whether the different fibers in these studies affected results. Regarding laser
26 generators, seven(63,97-102) used an Nd:YAG laser from an unspecified manufacturer,
27 one(103) used the Hercules 5060 Nd:YAG laser generator (Lasersonics, Tokyo, Japan),
28 one(96) used the Trimedynе Nd:YAG laser (Trimedynе, Irvine, CA, USA), and one(95)
29 used the SLT Nd:YAG laser (Surgical Laser Technologies, Oaks, PA, USA). As with the
30 fiber differences, because of the lack of controlled trials comparing generators, one
31 cannot determine whether device differences could have affected outcomes.

- 32 • **One year after surgery, symptoms and quality of life improvements are similar**
33 **after VLAP and TURP. VLAP requires shorter hospitalizations and longer**
34 **catheterization times than TURP. Two trials report that major adverse events**
35 **are less likely after VLAP than after TURP. Three trials report that patients**
36 **who receive VLAP are more likely to require retreatment than patients who**
37 **receive TURP.**

38 Ten trials (eight of them randomized) compared VLAP to TURP.(63,64,95-108)
39 The trials enrolled over 1,057 patients. One of these, the CLASP randomized trial,
40 also included a group of patients who received only “conservative management,” and
41 VLAP patients fared significantly better in symptom score improvement than those
42 patients.(100,105,109) Of eight studies reporting IPSS scores at 6-8 months of followup,

1 four(63,64,98,101,102) reported statistically significantly fewer symptoms after TURP
2 than after VLAP. None of the three studies reporting twelve month or longer followup
3 reported any statistically significant differences in IPSS scores.(63,64,95,97) Four of five
4 studies reporting quality of life data found no statistically significant differences between
5 VLAP and TURP.(63,64,96,100-102,104-108) Of five studies reporting peak urinary
6 flow rates at one year or longer, two(95,96,106-108) found no significant differences
7 between VLAP and TURP, and three(63,64,97,99) did not report statistical tests of this
8 outcome.

9 Of four trials reporting operation times, one study with multiple publications(96,106-108)
10 reported statistically significantly shorter operation times for VLAP than for TURP,
11 one study(95) reported no statistically significant difference, and the other two
12 studies(100,103-105) did not report statistical tests of this outcome. Of eight trials
13 reporting hospitalization times, five(95,96,100-102,104-108) reported that it was
14 statistically significantly shorter after VLAP than after TURP. Of eight trials reporting
15 catheterization times, four(63,64,100-102,104,105) reported that catheterization times
16 were statistically significantly longer after VLAP than after TURP. Of seven
17 trials(63,64,96,97,99-101,103-108) reporting rates of blood transfusion, one study with
18 multiple publications(96,106-108) reported statistical tests of this outcome, and it
19 reported no statistically significant difference.

20 Two trials reported that significantly fewer major adverse events (e.g., urethral stricture)
21 occurred in patients who receive VLAP than those who received TURP (8-11% VLAP
22 versus 30-36% TURP).(96,101)

23 Three prospective trials reported retreatment rates,(99,101,102) and they all found that
24 retreatment was more common after VLAP than after TURP (7-9% versus 0-4%,
25 respectively).

26 • **CLAP and VLAP yield similar improvements in symptoms and peak urinary**
27 **flow rates. The findings on retreatment rates are mixed.**

28 Three RCTs with one to two year followup compared CLAP to VLAP.(95,110,111)
29 Both treatments reduced symptoms in all three trials to a similar degree. Peak urinary
30 flow rate (Qmax) also improved similarly after both treatments.(95,110,111) Findings on
31 retreatment rates, reported by two trials, were mixed; Narayan, 1995(111) found that
32 0/32 (0%) CLAP patients required retreatment as compared to 5/32 (16%) of TURP
33 patients (statistically significant difference). Bryan (2000)(110) reported similar
34 retreatment rates after CLAP and VLAP (4.8%, or 1/21 patients versus 11.8% or
35 2/17 patients) but may have had insufficient statistical power to detect a difference
36 in retreatment rates.

37 Three trials reported catheterization time; although Bryan, 2000 found longer catheter
38 times after VLAP (13.2 days versus 4.5 days for CLAP)(110), the other two trials did not
39 find such differences (one to two days for both treatments).(95,111)

- 1 • **One RCT reported long-term results comparing VLAP to hybrid laser and**
2 **found similar results on symptoms, peak urinary flow rates, retreatment,**
3 **adverse events rates, and perioperative outcome measures for the two**
4 **treatments.**

5 One RCT (N = 93) with three-year followup compared VLAP with Urolase fiber to a
6 hybrid laser technique using the Ultraline fiber.(112-114) Symptoms, physiological
7 measures, retreatment, adverse events, and perioperative measures were all similar after
8 the two treatments.

9 **Holmium laser treatment**

10 *Technology Description and Clinical Issues*

11 Surgical use of the holmium laser for BPH has evolved since its original introduction in
12 1994. Initially, holmium laser ablation of the prostate (HoLAP) was performed and
13 involved the use of side-firing and end-firing laser fibers to vaporize and ablate prostate
14 tissue. Relief of obstruction is immediate, unlike other laser procedures such as VLAP in
15 which benefits are seen only after a delay. However, HoLAP does not yield tissue for
16 histologic analysis, therefore surgeons later developed holmium laser resection of the
17 prostate (HoLRP).

18 In HoLRP, the surgeon resects prostate tissue into pieces small enough to be removed
19 with bladder irrigation and grasping forceps or a modified resectoscope loop. Compared
20 to TURP, however, HoLRP yields less tissue for analysis, and the available tissue is of
21 lower quality due to thermal artifacts.(115) These problems, in addition to relatively long
22 operation times, motivated the development of Holmium laser enucleation of the prostate
23 (HoLEP) in conjunction with a tissue morcellator.

24 In HoLEP, an entire prostatic lobe can be separated from connective tissue and deposited
25 into the bladder. The removal of intact lobes is similar to open prostatectomy, discussed
26 above. The morcellator then extracts the tissue from the bladder without using heat,
27 thereby preserving tissue volume and quality. Bladder injuries related to careless
28 operation of the morcellator have been reported; distension of the bladder can prevent the
29 bladder mucosa from being drawn into the blades.(116) In the Findings section below,
30 the three Holmium procedures (HoLAP, HoLRP, and HoLEP) are discussed separately.

31 Prostate size is an essential factor in the choice of holmium laser procedures. For patients
32 with small prostates, HoLAP may still be appropriate,(116) and incision of the bladder
33 neck using the holmium laser is another alternative.(115) Moderately-sized prostates can
34 be treated with HoLRP.(117) One possible advantage of HoLEP is that with sufficient
35 surgical expertise, it can be applied to very large (>100 grams) prostates.(115)

36 An advantage of the holmium laser is the ability to coagulate tissue simultaneously with
37 tissue incision, vaporization, resection, or enucleation. This reduces intraoperative blood
38 loss as well as postoperative bleeding. However, holmium lasers are expensive, and the
39 surgical procedures generally require extensive training.(115-117) Therefore, fewer
40 urologists are likely to offer this treatment option to patients. A minimum of 20-30 cases

1 using HoLEP on small prostates may be necessary before a surgeon is sufficiently skilled
2 to treat patients with larger prostates.(116)

3 Many holmium lasers have been FDA approved for general urological indications.
4 Among them, specifically listing HoLEP, HoLAP, and HoLRP as intended uses, is the
5 Modified Lumenis VersaPulse PowerSuite Holmium and Dual Wavelength Surgical
6 Laser System.(FDA clearance product number K011703).(118) The system is indicated
7 for use in a variety of urological indications including BPH, lithotripsy, and tumor
8 removal. The FDA clearance did not mention whether the device was indicated for
9 patients with specific prostate sizes.

10 *Clinical Practice Guidelines*

11 The Fifth ICBPH favors the use of the holmium laser over CLAP and VLAP, although
12 they emphasized that there is a steep learning curve associated with holmium laser
13 use.(19) The ICBPH guidelines also stated that prostates larger than 100 grams are a
14 relative contraindication, but noted that the development of morcellators has improved
15 retrieval of larger prostate fragments from the bladder. The EAU guidelines recommend
16 laser prostatectomy using side-firing lasers or interstitial laser coagulation (ILC) for
17 patients who are on anticoagulant medication, who are not candidates for TURP, or who
18 desire to maintain ejaculation. The EAU noted that holmium laser resection/enucleation
19 is a promising technique with outcomes similar to TURP.(49) The AUA considers
20 holmium laser resection/enucleation an alternative to TURP in medical facilities that
21 have the technology and training.(3)

22 *Findings*

23 Holmium Laser Ablation of the Prostate (HoLAP)

24 The only study available evaluating HoLAP(119) used the VersaPulse Select laser
25 (Lumenis, Santa Clara, CA, USA). Two fibers were used: the Slimline 550 (Lumenis,
26 Santa Clara, CA, USA) or the Duo-Tome Sidelite (Lumenis, Santa Clara, CA, USA).

- 27 • **One controlled trial reported that symptoms and physiological measures**
28 **improve to a similar degree after HoLAP and TURP. This RCT also reported**
29 **that HoLAP operations take longer than TURP operations.**

30 One RCT (N = 36) compared HoLAP to TURP (Mottet et al. (1999)(119) with one-year
31 followup. Symptoms and physiological measures improved to a similar degree after both
32 HoLAP and TURP. However, this is based on only 36 patients.

33 Mottet et al. (1999)(119) found that HoLAP operations took statistically significantly
34 longer (mean 75 minutes) than TURP operations (mean 40 minutes), but they found
35 no differences in other perioperative measures. Enrollment may have been too low to
36 reliably detect differences in adverse events between HoLAP and TURP. Retreatment
37 data beyond six months after surgery were not reported.

1 Holmium Laser Resection of the Prostate (HoLRP)

2 All three trials of HoLRP used the VersaPulse pulsed holmium laser (Lumenis,
3 Santa Clara, CA, USA). One trial(86) used the Slimline fiber, and the other two(18,120)
4 did not specify the fiber that was used. No published controlled trials have compared the
5 use of different HoLRP devices. In general, however, the devices appear to be the same
6 or similar in different studies, which supports the grouping of these HoLRP studies.

- 7 • **One trial reported that HoLRP and TURP improve symptoms to a similar**
8 **degree and that HoLRP operations take longer than TURP operations. However,**
9 **HoLRP requires a shorter length of stay and catheterization time than does**
10 **TURP.**

11 One RCT (N = 120) compared HoLRP to TURP.(18,121,122) At two-year followup,
12 improvements in symptoms after HoLRP were similar to those after TURP.

13 These authors also reported statistically significantly longer operation times for HoLRP
14 (mean 41.5 minutes) than for TURP (25.3 minutes). However, patients who received
15 HoLRP experienced statistically significantly shorter hospital stays (mean 1.1 days vs.
16 2.0 days) and catheterization times (0.8 days vs. 1.6 days) than patients who received
17 TURP. The study also reported that two years after treatment, 8% of patients who
18 received HoLRP had required additional surgical treatment as compared to 12% of
19 patients who had received TURP (not statistically significantly different).

- 20 • **One trial reported that some physiological measures are significantly better after**
21 **HoLRP than after VLAP, but improvement in symptoms is similar.**
22 **Catheterization times are shorter after HoLRP than after VLAP.**

23 Two trials compared HoLRP to VLAP.(86,120) Gilling et al. (1998)(120) (N = 22) found
24 that some physiological measures were significantly better after HoLRP than after VLAP,
25 but reported that symptoms and postvoid residual volumes were similar after these two
26 treatments. The trial may not have been sufficiently powered to detect clinically
27 meaningful differences. Both trials reported that catheterization times were significantly
28 shorter after HoLRP than VLAP (1.4-1.9 days versus 9.0-11.9 days,
29 respectively).(86,120)

30 Holmium Laser Enucleation of the Prostate (HoLEP)

31 Both trials of HoLEP used the VersaPulse holmium laser and VersaCut Morcellator
32 (Lumenis, Santa Clara, CA, USA).

- 33 • **Two trials reported that after six months, HoLEP and open prostatectomy yield**
34 **similar symptom improvement in patients with large prostates. Two trials**
35 **reported that HoLEP required shorter hospital stays and one trial reported that**
36 **HoLEP required shorter catheterization times.**

37 Trials of HoLEP enrolled only patients with large prostates (>100 grams), and therefore
38 the control group surgical procedure was open prostatectomy. Two controlled trials
39 (N = 140) reported on this comparison.(123,124) At six months, symptoms and
40 physiological measures were similar after HoLEP and open prostatectomy.

1 Kuntz et al. (2002)(123) reported statistically significant longer operation times for
2 HoLEP than for open prostatectomy (mean 136 minutes versus 91 minutes). Moody et al.
3 (2001)(124) reported a difference in the same direction that was not statistically
4 significant (HoLEP 197 minutes, open prostatectomy 173 minutes). Both trials reported
5 that hospital stay was statistically significant shorter after HoLEP than after open
6 prostatectomy (2.1-2.9 days vs. 6.1-10.5 days).(123,124) One trial reported that
7 catheterization time was statistically significant shorter after HoLEP than after open
8 prostatectomy (1.28 days vs. 8.1 days).(123,124) In addition, fewer HoLEP patients
9 required blood transfusions (0% versus 13-30% for TURP).(123,124)

10 Both trials reported similar rates of adverse events for HoLEP and open prostatectomy,
11 but few (usually <5) patients experienced any given event. Therefore, the frequencies of
12 adverse events that were reported in these trials may not be reliable.

13 One trial reported that retreatment rates at six month followup were similar for HoLEP
14 and prostatectomy,(123) but no data from controlled trials are currently available on
15 long-term retreatment rates.

16 **Interstitial laser coagulation**

17 *Technology Description and Clinical Issues*

18 In interstitial laser coagulation (ILC), the physician inserts a fiberoptic laser probe
19 through a cystoscope into the prostate at fixed points. Laser energy is applied for
20 approximately three minutes to coagulate each area of obstructing prostate tissue,
21 producing necrosis. In contrast to other laser procedures, where coagulation necrosis
22 occurs at the urethral surface, in interstitial laser coagulation, delivery of laser energy
23 directly into the tissues produces coagulation necrosis inside the adenoma. The
24 postprocedural tissue sloughing that occurs following surface laser treatment does not
25 occur with ILC,(125) which may reduce the risk of urinary tract infection.(126)
26 The treated tissue then cavitates or is absorbed over a period of several weeks.

27 ILC can be performed in a physician's office or an outpatient surgery center using local
28 anesthesia and intravenous sedation. The ILC procedure takes approximately 30 to
29 60 minutes, depending on the number of areas to be treated. Postprocedure
30 catheterization is required for 7 to 21 days. The use of laser energy minimizes the risk of
31 bleeding. However, like most other laser procedures, ILC destroys tissue, not reserving
32 any for histological examination, and thus requires physicians to take pretreatment
33 samples in patients at risk for prostate cancer.(127)

34 ILC was first developed using the Nd:YAG laser of 1,024 nm, but has since been
35 modified for use with diode lasers of 805 to 980 nm.(126) Standard treatment protocol
36 begins with the laser firing with 20 watts of energy, gradually decreased to about 7 watts.
37 The applicator may allow laser energy to be emitted in all directions, or only
38 circumferentially forward.(126) It is unclear from the small literature base whether these
39 different technologies affect the efficacy of ILC; therefore, we discuss the reported
40 efficacy of ILC as a group, which conforms to the way the procedure is categorized by
41 clinicians in the literature. There are no published controlled trials comparing the efficacy

1 of individual ILC devices. The only application difference that we call out in our
2 discussion is a single controlled trial of low-powered ILC, in which the initial wattage is
3 lower than in the traditional protocol.(128) FDA cleared lasers used in ILC include the
4 Ethicon Indigo 830e and Dornier’s MediLas H. The use of these lasers is generally
5 indicated for men over 50 years old with symptoms of BPH and prostatic lobes sizes of
6 28-85 cc.

7 *Clinical Practice Guidelines*

8 The Fifth ICBPH rated ILC an “acceptable” procedure for BPH.(19) The AUA considers
9 ILC an “emerging therapy” and states that additional data are required before it can be
10 recommended as a treatment option. However, they state that ILC may be offered to
11 appropriate patients provided that the uncertainty of ILC outcomes relative to
12 recommended treatments are discussed with the patient.(3)

13 *Findings*

14 Two of the five trials comparing ILC to TURP reported the device used: one trial used
15 the Medilas 4199 Fibertom Nd:YAG laser (Dornier MedTech, Kennesaw, GA USA) at a
16 wavelength of 1,064 nm. Wattage was varied from 20 W down to 7 W.(129) The second
17 trial used the Dornier ITT thermotherapy fiber (Dornier MedTech), from 20W down to
18 7.5 watts.(127)

19 The other three studies did not specify what device was employed, but two of them
20 reported starting the treatment at 20 watts.(43,126) Without further information or
21 comparison among devices, we assume that this class of devices can be considered
22 together.

- 23 • **ILC and TURP generally provide similar improvements in symptoms and**
24 **quality of life. Results for physiological measures were mixed. Two trials**
25 **reported higher retreatment rates after ILC. Unlike TURP, ILC may not**
26 **require any hospitalization time, but this may be offset by a longer**
27 **catheterization time.**

28 Two RCTs and three non-randomized controlled trials (N = 496) compared ILC to
29 TURP.(43,126,127,129,130) In general these trials reported similar results for ILC and
30 TURP in symptoms (IPSS) and quality of life; however, one study reported that DANPSS
31 symptom and bother scores were higher (worse) after ILC than after TURP.(129) One
32 trial asked patients about satisfaction with treatment: while 56% of TURP patients
33 reported being “completely satisfied,” only 24% of ILC patients reported the same.(129)

34 Results for physiological measures were mixed; two RCTs found that peak urinary flow
35 (Qmax) was similar after ILC and TURP,(43,129) while two non randomized trials found
36 Qmax to be better improved after TURP (statistical significance not reported).(126,127)
37 One RCT and one non-randomized trial reported that post-void residual volume (PVR)
38 was similar after both treatments,(43,127) while one RCT and one non-randomized trial
39 found that PVR was higher after ILC (statistically significant in the RCT).(126,129)

1 The two trials that reported retreatment rates for ILC and TURP both found higher rates
2 for ILC (7-16% ILC versus 0-3.5% TURP) (statistical significance not reported).(43,127)
3 However, both studies had a small number of patients in the ILC group (N = 30 to 37),
4 and the overall number of patients undergoing retreatment were very low (<4 per group).
5 This low statistical power may result in unreliable event rate estimates.

6 Two RCTs reported that ILC had higher rates of urinary tract infections (UTI) (statistical
7 significance not reported), (20-61% ILC versus 11-14% TURP)(43,129) while one non-
8 randomized trial reported that ILC was associated with a lower rate of UTI (7% versus
9 13% for TURP).(127) Because these were not large trials, estimated event rates may not
10 be reliable, especially for those events occurring with low frequency.

11 In the three studies reporting hospitalization time (two RCTs and one non-RCT), ILC had
12 a shorter hospitalization time than TURP (and in the United States, may almost always be
13 performed on an outpatient basis(131)),(43,127,129) but one non-randomized trial
14 reported that ILC requires several days of catheterization instead (mean: 14 days versus
15 3.5 days).(127)

- 16 • **Two trials reported that ILC and transurethral microwave therapy (TUMT)**
17 **yield similar symptom improvements, but that ILC provided higher peak**
18 **urinary flow rates. One RCT also reported that ILC was associated with a**
19 **higher rate of adverse events than TUMT.**

20 Two trials, Norby et al. (2002) and Arai et al. (2000) (N = 182) compared ILC to
21 TUMT.(129,130) Norby's randomized trial reported similar symptom improvements for
22 ILC and TUMT at 6 months and slightly more improvement in peak urinary flow rate
23 (Qmax) with ILC (statistical significance not reported).(129) The Arai trial, which was
24 not randomized, reported significantly greater improvements with ILC for symptoms,
25 Qmax and QoL; however, the study was not randomized and had only 3 months'
26 followup.(130)

27 Norby reported in general that there were more adverse events after ILC than after
28 TUMT, including UTI (61% versus 30%), re-retention (9% versus 2%), retrograde
29 ejaculation (35% versus 22%), and decreased erectile capacity (29% versus 9%)
30 (statistical significance not reported). In one trial, ILC required a mean of 3 days of
31 hospitalization, versus no hospitalization for TUMT.(129)

- 32 • **One non-randomized controlled trial reported that ILC resulted in better**
33 **symptomatic, quality of life, and physiological improvements than radio**
34 **frequency needle ablation (RFNA).**

35 Arai et al. (2000),(130) (N = 88), was the only trial to compare ILC to RFNA (also
36 known as TUNA®), in a non-randomized prospective trial. After three months, ILC was
37 found to be significantly superior to RFNA in terms of IPSS scores, quality of life, and
38 post-void residual volume. Similar improvements were noted for the two groups in terms
39 of BPH Impact Index and maximum urinary flow. Retreatment rates were not reported.

1 • **One non-randomized controlled trial reported that ILC resulted in similar**
2 **symptomatic improvements to hybrid laser, and a lower retreatment rate.**
3 Pypno et al. (2000) (N = 142), compared ILC to both hybrid laser (VLAP) and TURP.
4 Only 30 patients were included in the ILC treatment group, which limits the statistical
5 power of this comparison. In looking only at results up to six months when most patients
6 were still enrolled, symptom scores, Qmax, and post-void residual volume were all
7 similarly improved in both groups. After a mean 23 months of followup, more hybrid
8 laser patients required retreatment than did patients receiving ILC (15% versus 7%).(127)
9 No statistical analyses were provided to validate any of the patterns observed.

10 • **One RCT reported that low-energy ILC is not as effective as TURP in terms of**
11 **symptoms, quality of life, or physiological measures. This one trial also reported**
12 **that while low-energy ILC has a lower rate of retrograde ejaculation than**
13 **TURP, UTI rates were similar for the two treatments. One trial reported that**
14 **catheterization time was longer after ILC.**

15 Martenson et al. (1999)(128) (N = 44) compared ILC using a diode laser to apply low
16 energy (10 watts maximum, device not described) to TURP. Results suggested that
17 low-energy ILC was not as efficacious as TURP in terms of most quality of life,
18 symptoms, and physiological measures. It was associated with a lower rate of retrograde
19 ejaculation (42% versus 75%). Catheterization time was 27 days for ILC versus 3 days
20 for TURP, not offset by the reported hospitalization times (2.3 versus 3.8 days).
21 (However, ILC is almost always performed on an outpatient basis in the United
22 States,(131) therefore these statistics may not be representative of general practice.)
23 Twenty percent of patients (6 patients) were retreated in the low-ILC group, versus
24 7% (one patient) in the TURP group (not a statistically significant difference in this low-
25 powered trial).

26 **Hybrid laser techniques**

27 *Technology Description and Clinical Issues*

28 Hybrid laser procedures involve the use of one or more laser techniques, types, and
29 power settings to treat BPH. For example, one hybrid technique uses non-contact VLAP
30 with an Nd:YAG laser and sidefiring fiber to coagulate prostate tissue followed by CLAP
31 using a contact laser probe to vaporize the tissue. Another hybrid technique uses a KTP
32 laser at 34 W for bladder neck incision followed by Nd:YAG coagulation at 60 W.

33 Hybrid laser techniques were developed to reduce side effects associated with certain
34 laser wavelengths. Using a KTP/Nd:YAG hybrid technique, for example, allows the
35 surgeon to vaporize sections of Nd:YAG coagulated tissue with the KTP laser to reduce
36 the likelihood of prolonged postoperative urinary retention and catheterization.

37 These techniques employ the same devices as other laser techniques, thus the same
38 FDA 510(k) clearances for marketing apply.

39 *Clinical Practice Guidelines*

40 No current clinical practice guidelines discuss hybrid laser techniques.

1 *Findings*

2 Seven controlled trials (N = 961; published in 11 reports) have investigated hybrid laser
3 techniques.(109,112,127,132-139) Four trials compared a hybrid laser technique to
4 TURP, and three trials compared a hybrid laser technique to other surgical procedures.

5 Three studies(91,109,135) used the ADDstat fiber (Laserscope, San Jose, CA, USA),
6 one(112) used the Urolase fiber (Bard, Covington, GA, USA), one(139) used three
7 different fibers (SideFire, Slimline, and DuoTome SideLite, all manufactured by
8 Lumenis, Santa Clara, CA, USA), and two(127,133) did not report the specific type(s) of
9 laser fibers. Also, the seven controlled trials used six different laser generators; these
10 included the VersaPulse Select laser (Lumenis, Santa Clara, CA, USA),(139) the
11 Nd:YAG/KTP laser (Laserscope, San Jose, CA, USA),(109,135) the KTP/YAG XP laser
12 (Laserscope, San Jose, CA, USA),(137) the Nd:YAG Medilas 4060 Fibertom laser
13 (Dornier, Munich, Germany),(127) the SLT Nd:YAG laser (Surgical Laser Technologies,
14 Oaks, PA, USA),(133) and an Nd:YAG laser from an unspecified manufacturer.(112)

- 15 • **Hybrid laser techniques are too varied to permit general conclusions about this**
16 **category of treatment for BPH.**

17 **Comparisons between hybrid laser techniques and TURP**

18 In one trial (N = 100), surgeons first vaporized the prostatic fossa using a KTP laser, and
19 then performed VLAP using an Nd:YAG laser to create craters in the lateral
20 lobes.(109,132,137,138) The authors reported that symptoms, physiological measures,
21 and retreatment rates were similar for the hybrid laser technique and TURP at three to
22 six years' followup. Two other trials, one randomized and one not, (N = 275) compared
23 outcomes of patients who received TURP to those who received a hybrid technique
24 consisting of VLAP followed by CLAP.(127,133,134) The authors of both trials reported
25 that patients fared better after TURP.

26 A fourth trial (N = 204) used a hybrid technique with the KTP laser for vaporization and
27 then the VLAP-free paint technique for coagulation, compared to TURP.(112,120)
28 At one year after treatment, authors reported no differences between patients who had
29 this hybrid technique and the patients who had received TURP.

30 These four trials suggest that the techniques and results for comparison of hybrid laser to
31 TURP have varied too widely to consider the studies as a group to reach conclusions
32 about one "hybrid" technique.

33 **Comparisons between hybrid laser techniques and other surgical procedures**

34 One trial (N = 31) compared outcomes after TUEVP to those after the KTP/VLAP
35 technique described above, (137,138) and reported similar outcomes at six months with
36 respect to symptoms, physiological measures, and adverse events. However, the authors
37 did report that operation time was shorter for the hybrid laser technique than for TUEVP.

38 A non-randomized trial (N = 142) compared the perioperative outcomes of a combined
39 technique of HoLAP and VLAP with those of HoLAP alone, and reported shorter

1 catheterization times and lower recatheterization rates for patients receiving HoLAP
2 alone.(136)

3 One RCT compared VLAP with the Urolase fiber to those after CLAP/VLAP with the
4 Ultraline fiber.(135) Authors reported no significant differences between the two laser
5 techniques at three years after treatment.

6 As with the comparison to TURP, again this literature demonstrates a wide variety of
7 hybrid techniques that preclude coming to conclusions about hybrid laser treatment as a
8 single group.

9 **Photoselective vaporization of the prostate (PVP)**

10 *Technology Description and Clinical Issues*

11 PVP uses a potassium-titanyl-phosphate (KTP) laser at 80 watts to vaporize prostate
12 tissue. PVP has been under investigation for about five years, and the first commercially
13 available PVP laser system for BPH treatment was introduced in early 2002.(140) PVP
14 was developed in response to the side effects associated with the deep tissue coagulation
15 produced by Nd:YAG lasers. KTP laser wavelengths penetrate only 1 to 2 mm, and the
16 vaporization process may help avoid the perioperative side effects (such as tissue
17 sloughing) of other laser surgical procedures. Another potential advantage of PVP is low
18 blood loss, which can be a problem with TURP.

19 The PVP procedure lasts from 20 to 50 minutes, depending on prostate size, and is
20 performed using local anesthesia, intravenous sedation, or general anesthesia on an
21 outpatient basis or with an overnight stay.(140) PVP has been used to treat prostates up to
22 120 grams in size.

23 PVP using the Lyra G Series Surgical Laser System (Laserscope, San Jose, CA) has
24 received FDA 510(k) clearance to be marketed for the treatment of BPH. The approval
25 documentation did not mention specific indications for prostate size.

26 *Clinical Practice Guidelines*

27 Since it has only recently been introduced, PVP was not addressed in the Fifth ICBPH,
28 EAU, and AUA guidelines. We identified no other guidelines addressing this technology.

29 *Findings*

30 Our searches identified no controlled comparisons of PVP to sham or to other treatments.

1 **Minimally Invasive Treatments**

2 **Transurethral radiofrequency needle ablation (RFNA or TUNA®)**

3 *Technology Description and Clinical Issues*

4 RFNA (marketed in the United States under the trade name, TUNA®) is a minimally
5 invasive technique that uses low-level radiofrequency (RF) energy to ablate selected
6 areas of prostate tissue. An RFNA system consists of a computerized RF generator and a
7 urethral catheter with two needles at the tip. The needles can be deployed in the urethra
8 independently, and can be positioned at either lateral lobe of the prostate. The RF
9 generator produces a dual 465 kilohertz RF signal that is transmitted through the catheter
10 to each of the needles to deliver energy at a power between 2 W and 15 W, thereby
11 heating the defined tissue area to produce coagulative necrosis. Thermosensors located in
12 the protective nylon shields of the needles and in the side of the catheter tip monitor
13 temperatures at the periphery of the treated area and in the urethra. The TUNA® system
14 has a safety feature that will automatically shut off the RF signal when the tissue
15 impedance exceeds 400 ohms or the urethral temperature exceeds 46 degrees
16 Celsius.(141,142) The amount of tissue ablation is determined by the length of the
17 needles (tissue contact), power delivery, and treatment duration.(143)

18 RFNA has been used for prostates ranging in weight from 15 to 100 grams.(144)
19 The procedure takes approximately 45 minutes and can be usually performed in a
20 physician’s office or as an outpatient procedure with topical or local anesthesia, although
21 some patients may require additional sedation.(145) Patients are able to return to most
22 normal activities within 24 hours.(146)

23 Medtronic Corporation manufactures the TUNA® system and is the only company with
24 FDA clearance to market such a system in the United States. It is cleared for use in men
25 over the age of 50 years with prostate volume of 20-50 cc, who are experiencing
26 symptoms due to urinary flow obstruction secondary to BPH.

27 *Clinical Practice Guidelines*

28 The Fifth ICBPH has noted that RFNA could become a “treatment of choice” for
29 relieving BPH symptoms in elderly patients at high surgical risk. However, they
30 emphasized that patient selection and degree of obstruction are critical factors, since
31 RFNA appears to be effective for patients with mild to moderate obstruction, but results
32 have been less than satisfactory for patients with more severe obstruction.(19)

33 In 2001, the EAU concluded that RFNA is a “simple and safe technique,” but does not
34 recommend it as a first-line treatment for patients with BPH due to treatment failure
35 rates.(49) In 2003, the AUA concluded that RFNA is an effective treatment for partially
36 relieving BPH symptoms (though not as effective as TURP), and that the ideal patient has
37 obstructive BPH, predominantly lateral lobe enlargement, and a prostate size of 60 grams
38 or less.(3)

1 *Findings*

2 Few details are provided by the available articles on the devices and techniques used to
 3 perform RFNA. None of the published trials appeared to use the FDA cleared TUNA®
 4 system, and it is not clear whether there are clinically meaningful differences among
 5 techniques. Without any direct comparison of techniques, we assume they are similar and
 6 discuss all four studies as a group.

7 Two randomized controlled trials (Bruskewitz et al. 1998; Mostafid et al., 1997) and
 8 two non-randomized comparative studies (Arai et al., 2000; Schatzl et al. 2000),
 9 (N = 330) compared RFNA (using the TUNA system) to TURP.(63,64,130,147-149)⁴

10 Schatzl also compared RFNA to TUEVP, HIFU, and VLAP, while Arai also compared it
 11 to ILC and TUMT. However, in both these latter studies, patients were often assigned to
 12 a treatment out of personal preference or based on physiological variables; thus,
 13 treatment groups may not be comparable. The Schatzl study also has limited statistical
 14 power (approximately 15 patients per treatment group), and may not be able to identify
 15 clinically significant differences between the groups.

- 16 • **RFNA results in less symptom and physiological improvement than TURP up to**
 17 **24 months after treatment, and two trials reported that the two treatments have**
 18 **similar effects on quality of life. One trial reported that decreased ejaculate and**
 19 **retrograde ejaculation occur less often after RFNA than after TURP.**

20 Bruskewitz et al (1998)(147,148) (N = 121) and Mostafid et al. (1997)(149) (N = 50),
 21 both randomized controlled trials, found that IPSS scores and Qmax improved
 22 significantly more after TURP than after RFNA. In the Bruskewitz trial (1998)(147,148)
 23 these differences did not become apparent until 12 months after treatment. One trial
 24 reported that quality of life scores were similar; 50% or better improvement in the AUA
 25 bother score occurred in 65% (38/59) of RFNA patients and 75% (35/47) of TURP
 26 patients (not statistically significant).(147)

27 The results from the study of Arai et al. (2000),(130) a non-randomized prospective trial
 28 (N = 116), generally agree with the findings of the above two RCTs.

29 All four trials reported some adverse events. In the largest RCT (N = 121), Bruskewitz
 30 reported that all adverse events occurred less often after RFNA than after TURP
 31 (statistical significance not reported): decreased ejaculate occurred in 13% of RFNA
 32 patients and 54% of TURP patients; bleeding occurred in 32% and 100%, respectively;
 33 erectile dysfunction in 0% and 13%; and retrograde ejaculation in 0% and 38%.(147,148)

34 The Mostafid and Schatzl trials enrolled too few patients to provide reliable adverse
 35 event rates. They report the occurrence of UTI, dysuria, and urinary retention in the
 36 RFNA group, and blood transfusion, UTI, and urinary retention in the TURP
 37 group.(64,149) Arai et al. (2000) reported only sexual complications; the authors asked

⁴ Bruskewitz and colleagues have recently published follow-up data to their 1998 study following patients to five years (Hill et al., 2004), but results beyond two years had a high attrition rate (>30%) and cannot be considered reliable.(150)

1 patients about ejaculation after treatment; significantly more patients undergoing TURP
2 had had no ejaculate or severely or moderately decreased ejaculate after treatment (69%
3 vs 46%, statistically significant).(130)

4 Bruskewitz (1998) reported that operation time was similar for RFNA and TURP (mean
5 42 and 53 minutes, respectively). All 56 TURP patients required catheterization while
6 only 40% (26/65) of RFNA patients did (statistical significance not reported).(147,148)
7 Hospitalization was slightly shorter for the RFNA group according to Bruskewitz and
8 Schatzl (1-1.5 days for RFNA and 2.1-4.3 days for TURP).(63,64,147,148) More patients
9 in the TURP group required blood transfusions (14%, or 3/22 versus 0%, or 0/20) in the
10 Mostafid trial (statistical significance not reported).(149)

11 There are not enough data from controlled trials to determine rates of retreatment.

- 12 • **One non-randomized trial reported that RFNA and TUMT provide similar**
13 **results, although patients may be more satisfied with RFNA. One trial reports**
14 **that RFNA is not as effective as ILC.**

15 Two studies (N = 185) compared RFNA to a variety of competing minimally invasive
16 surgeries.(63,64,130) One study by Schatzl (2000)(63,64) (N = 46) compared RFNA to
17 TURP, TUVF, HIFU, and VLAP. However, sample sizes for each treatment group were
18 small (n≤15), so this study may not have had the power to detect statistically significant
19 differences. Patients were also not randomized to treatment, which may have resulted in
20 non-comparable groups.

21 In another non-randomized trial, Arai et al. (2000)(130) (N = 139) compared RNFA to
22 both ILC and TUMT. Subjective measures improved after both RFNA and TUMT,
23 although physiologic measurements showed no significant change. When asked about
24 satisfaction with treatment, 23 out of 42 (55%) RFNA patients and 8 out of 40 (20%)
25 TUMT patients were “delighted” or “pleased” (statistical significance not reported).

26 **High-intensity focused ultrasound (HIFU)**

27 *Technology Description and Clinical Issues*

28 HIFU is a minimally invasive procedure that uses a transrectal ultrasound probe to image
29 the prostate and then heat tissue to 70 degrees to 90 degrees Celsius without harming
30 adjacent healthy tissue. The physician uses ultrasound guidance to position the HIFU
31 transducer and ensure that the prostatic urethra and bladder neck are in the treatment
32 zone. The transducer is designed to rotate laterally to treat seven to nine areas of the
33 prostate. HIFU treatment causes coagulative necrosis of the prostate tissue. In contrast to
34 other treatments, the HIFU device is inserted rectally and so does not contact the prostate
35 or urethra. This eliminates risks associated with device-related urethral and intraprostatic
36 manipulation.

37 The outpatient HIFU procedure usually takes less than three hours, and is performed
38 under general or spinal anesthesia, or intravenous sedation, depending on the patient.
39 Postprocedure catheterization time ranges from a few days to over a week.

1 The ultrasound device (Focus Surgery Sonoblate 500) used for HIFU treatment of the
2 prostate is currently under investigation in the United States, and is not approved or
3 cleared by the FDA for marketing.(151)

4 *Clinical Practice Guidelines*

5 The EAU does not recommend HIFU for elderly patients.(49) Information about HIFU
6 was not included in the 2000-2001 Fifth ICBPH proceedings. The AUA considers HIFU
7 an “investigational therapy” that should only be offered in the context of a clinical
8 trial.(3)

9 *Findings*

- 10 • **Only one study examined HIFU, but it was not randomized, and patients in its**
11 **groups were not comparable.**

12 A trial by Schatzl et al (2000)(63,64) was the only comparative study of HIFU.
13 It compared HIFU to TURP, TUEVP, VLAP and RNFA. Randomization was attempted,
14 but could not be carried out, because patient characteristics such as prostate size,
15 prostatic calcifications and middle lobes limited the types of patients who could receive
16 the different treatments. The patients who received HIFU tended to have smaller
17 prostates and less severe symptoms than those who received TURP. Results may be
18 influenced by these differences in patients, and are not considered further.

19 **Transurethral microwave thermotherapy (TUMT)**

20 *Technology Description and Clinical Issues*

21 TUMT is a nonsurgical, catheter-based treatment that uses radiant microwave heating to
22 ablate prostate tissue. The microwave generator delivers energy through a urethral
23 catheter to heat the prostate tissue to between 45 degrees and 55 degrees Celsius, and the
24 heating process causes necrosis (localized tissue death) of the prostate tissue that is
25 obstructing the urethra. It is performed on an outpatient basis and usually takes about an
26 hour. Postoperative catheterization times can range from a few days to several weeks,
27 depending on the degree of prostatic edema.(6) Because it does not cut out tissue, there is
28 no reserved tissue for histological examination for prostate cancer.

29 Although all TUMT devices are designed to deliver microwave energy to the prostate via
30 a urethral catheter, currently manufactured devices differ on a variety of technical details.
31 For example, the standard TUMT method, no matter which device is used, generally
32 takes about one hour to perform. However, two devices have been introduced or modified
33 recently to perform the procedure in about 30 minutes.(152,153) There are currently no
34 published controlled trials about the efficacy of these 30 minute protocols. Although it is
35 possible that individual devices and protocols may differ in level of efficacy, there is
36 no published evidence from controlled trials comparing different TUMT devices in terms
37 of patient outcomes.

38 Another difference among some TUMT devices is their intended patient population.
39 Some manufacturers state that their devices are for patients with “symptomatic” BPH,
40 and work by heating and destroying prostate tissues (e.g., Prostatron 2.0). Other

1 manufacturers state that their devices are for patients with “obstructive” BPH and
2 focus the thermotherapy on the bladder neck where the obstruction occurs
3 (e.g., Prostatron 2.5).(154)

4 One major delineation between different TUMT devices is the presence or absence of a
5 cooling mechanism. There are four TUMT devices market approved by FDA that
6 incorporate a urethral cooling device that protects the urethra from the extreme
7 temperatures used to destroy prostatic tissue, and are intended to provide a more tolerable
8 level of pain to the patient.(155) These are the Targis® and Prostatron® (2.0 and 2.5),
9 both manufactured by Urologix, Inc., the Prolieve™ manufactured by Celsion
10 Corporation (on which no published data are yet available), and the Urowave®
11 manufactured by Dornier, Inc. (The Urowave is not currently marketed within the
12 United States.) Two other devices marketed within the U.S. (TherMatrx TRX-2000;
13 Prostalund CoreTherm™) do not incorporate a cooling mechanism, under the supposition
14 by the manufacturers that such a mechanism did not achieve its goal of patient tolerance,
15 and as a result requires heavy patient sedation, which has potential side effects. The non-
16 cooling devices are reported to require only light patient sedation.(155)

17 Grouping TUMT devices based on the presence or absence of a cooling mechanism is a
18 widely accepted classification in the industry. Given the technical differences between
19 cooling and non-cooling devices, we consider the results from trials on these two classes
20 of TUMT device separately.

21 We discuss the reported efficacy of all cooling devices as a single group, and there is
22 no published evidence from controlled trials that the individual devices differ in any
23 clinically significant way. The same holds true for the non-cooling devices, although
24 less evidence is available on this newer technological approach.

25 Treatment efficacy may also be affected by the intraprostatic temperature achieved
26 during treatment.(156) The target temperature of the prostate during TUMT has been
27 reported in clinical trials to range from 45 to 55° C. However, details on target or
28 maximum allowed temperature were scarce in the literature, thus precluding us from
29 analyzing results based on this treatment characteristic. There appear to be no trials that
30 have analyzed the target temperature and its effect on clinical outcomes after TUMT.

31 The wattage used to attain therapeutic prostatic temperatures may also affect the
32 performance of the device, as different devices are designed to use different power levels.
33 For example, while the Prostatron 2.5 can deliver up to 70 watts of energy, the Thermatrx
34 2000 delivers only 7 watts. The lack of a cooling mechanism in the Thermatrx device
35 may allow it to heat the tissue as quickly to high temperatures as do cooling devices, even
36 though the actual amount of power used is much lower. We were able to locate only a
37 single, non-randomized controlled trial in the published literature (Rivas et al., 2000) that
38 compared higher and lower-wattage devices in terms of clinical outcomes; however, in
39 this study, patients with smaller prostates were more likely to be assigned to the low-
40 power group, and those with large prostates to the high-power group.(157) Thus, these
41 results may be unreliable. Hence, we have no information on how the wattage of the

1 device may affect the outcomes of treatment, and do not analyze results based on energy
2 level.

3 The specific design and performance characteristics of the antenna used to deliver the
4 microwave energy to the prostate may also play a critical role in achieving therapeutic
5 intraprostatic temperatures during TUMT, and one laboratory study has shown that
6 different device antennas do provide different patterns of energy to the targeted
7 tissue.(156) However, such findings have not been directly linked to clinical outcomes,
8 and therefore such device specifications are not addressed further in our consideration of
9 the evidence on TUMT.

10 In October 2000, the U.S. Food and Drug Administration issued a hazard warning for
11 TUMT based on reports of thermal injuries that required subsequent colostomies, partial
12 amputation of the penis, or other interventions. According to FDA,(158) these injuries
13 may take hours or days to become apparent, and are a result of incorrect device
14 placement or migration, balloon leakage, failure to pause treatment when the patient
15 signals pain, oversedation of the patient, treatment of prostates larger than those specified
16 in product labeling, and treatment of patients who have undergone pelvic radiation
17 therapy. This warning appears to apply to cooling TUMT devices, which were the most
18 common TUMT devices on the market at the time of the hazard warning. No such
19 adverse events were reported in the clinical trials considered in this report below;
20 however, clinical trials may provide more rigorously controlled treatment methods than
21 are performed in general practice.

22 *Clinical Practice Guidelines*

23 In 2001, the World Health Organization Committee on Interventional Therapies
24 recommended the use of TUMT as a minimally invasive treatment alternative for
25 BPH.(38,48) The EAU guidelines recommend TUMT for patients with larger prostates
26 and higher grades of bladder outlet obstruction, and for patients who wish to avoid
27 surgery or who no longer respond favorably to medical management.(49)

28 The Fifth ICBPH stated that TUMT is a viable BPH treatment that has “gained a firm
29 place in the urologist’s armamentarium.”(19) In addition, the ICBPH highlighted the
30 importance of mapping intraprostatic temperature during TUMT to avoid thermal injury,
31 and that TUMT systems should have some method of assessing temperature during
32 treatment.(19) All FDA-cleared devices considered in the present report have built-in
33 temperature monitors and safety shut-off mechanisms intended to prevent unnecessary
34 thermal damage.

35 The AUA concluded that TUMT is effective in partially relieving BPH symptoms, and
36 that no commercial device is superior to another, because their literature searches found
37 no direct comparator trials of commercial devices.(3) ECRI concurs that no such
38 comparison trials are available currently in the published literature, up to May 2003.

1 *Findings*

2 Here, we present results from trials of cooling and non-cooling devices separately, as this
3 is an accepted delineation in the industry, and because no other clinical data exist that
4 would support an alternative approach for examining differential efficacy of the devices.
5 We focused on trials that provided technical information about the devices they used, or
6 used a device approved for marketing by FDA. We do not discuss studies that did not
7 identify the type of device used.(159-167)

8 Thirteen of the 15 relevant controlled trials we identified randomized patients to
9 treatment groups (RCTs),(129,159,168-179) and two were non-randomized controlled
10 trials.(130,157)

11 Cooling TUMT

12 • **Cooling TUMT leads to improved symptoms and physiological measures up to**
13 **12 months after treatment.**

14 Five sham-controlled trials (N = 674), all of which blinded patients to treatment,
15 evaluated TUMT devices that employed a urethral cooling mechanism (Targis;
16 Prostatron; Urowave).(159,168-172) All trials were randomized. Four (N = 554) found
17 cooling TUMT to be significantly more effective than a sham treatment in terms of
18 symptoms and physiological measures.(159,168-171) Results on TUMT's effects on
19 quality of life were mixed. A fifth trial (Nawrocki et al., 1997, N = 120) found similar
20 results on all outcome measures for the sham and TUMT groups. Through an analysis
21 with an additional no-treatment group, the authors attributed many improvements
22 exhibited by both the TUMT and the sham groups to a placebo effect.(172)
23 Improvements may also have been due to the placement of the catheter by itself.

24 Although individual devices may differ in technical specifications, it appears from the
25 above trials that cooling TUMT devices show the same general trend of results.

26 Given that cooling TUMT has been found to be generally more effective than a sham
27 treatment (although the precise reason for its efficacy is unclear), it is important to
28 determine whether it offers any advantages over TURP, the current standard of care.
29 The most obvious advantage of TUMT is that it is performed on an outpatient basis under
30 mild sedation. Thus, TUMT is initially less invasive than TURP in the patient's daily life.

31 • **Most trials report that cooling TUMT provides less symptom relief and less**
32 **improvement in physiological measures than does TURP. One trial reported that**
33 **retrograde ejaculation was less common after TUMT than after TURP.**
34 **Retreatment rates may be higher after cooling TUMT than after TURP.**

35 Five RCTs and one non-randomized controlled trial (N = 514) compared cooling TUMT
36 to TURP.(129,130,173-176,180-182) Three trials on recent models of the
37 Prostatron(129,173,174,180-182) (N = 267) reported that symptoms improved
38 significantly less after TUMT than after TURP. In one trial, more TURP patients
39 expressed satisfaction with treatment after six months (54% vs 16% for TUMT).(129)

1 However, two older trials (N = 132) using earlier versions of Prostatron(175,176) found
 2 TURP to be more effective than TUMT on physiological outcome measures such as
 3 Qmax, but reported that the two technologies resulted in similar scores most symptom
 4 scales, such as IPSS and Madsen-Iverson.

5 Adverse events may be more severe after TURP than after cooling TUMT; however, the
 6 only device for which adverse event data are available is the Prostatron. Ahmed et al.
 7 (1997) reported that more TURP patients experienced retrograde ejaculation after
 8 treatment than did TUMT patients (63% versus 22%).(175) Dahlstrand et al. (1995)
 9 reported more “late complications” after TURP than after TUMT (13% versus 0%).(176)
 10 Norby et al. (2002)(129) reported that the most common adverse event for TURP or
 11 TUIP was retrograde ejaculation (50% of patients questioned) and for TUMT, UTI (30%
 12 of patients evaluated).

13 Three trials evaluating Prostatron 2.0 (60W) or 2.5 (70W) reported that retreatment rates
 14 may be higher after cooling TUMT than after TURP.(174,176,180) At 36 months,
 15 Floratos et al. (2001) employed Kaplan-Meier statistics to estimate the retreatment rate
 16 to be 20% for the TUMT group and 13% for the TURP group (not statistically
 17 significant).(180) At 30 months, D’Ancona et al. (1998) reported a similar pattern, with
 18 retreatment rates of 26% (8/31) for the TUMT group and 10% (2/21) for the TURP group
 19 (statistical significance not reported).(174) At 24 months, Dahlstrand also reported that
 20 retreatment rates tended to be higher after cooling TUMT (11%, 4/37 patients) than after
 21 TURP (0/32 patients) (statistical significance not reported).

22 • **One trial reported that cooling TUMT yielded more improvements in symptoms,
 23 quality of life, and peak urinary flow rate than alpha-blockade medication.**

24 In a single randomized controlled trial (N = 103), Djavan et al. (2000)(179) compared
 25 cooling TUMT using the Targis device to the alpha-blockade drug, Terazosin, given in
 26 increasing doses (from 1 to 5 mg) for 24 days. Patients in this trial had moderate to severe
 27 LUTS. The authors postulated that TUMT might provide a viable treatment to delay
 28 symptom onset compared to alpha blockades, which have side effects. Over six month
 29 followup, patients showed greater improvements in the TUMT group as measured by
 30 symptom scales (IPSS), quality of life, and peak urinary flow rate. The actuarial failure
 31 rate was significantly lower in the TUMT group (6% versus 41%). Adverse events
 32 experienced by patients undergoing TUMT included UTI and loss of ejaculate (exact
 33 rates not reported). The Terazosin patients experienced dizziness, asthenia, and
 34 headaches (exact rates not reported).

35 • **Two trials provided mixed results as to the relative efficacy of cooling TUMT
 36 compared to ILC, suggesting that TUMT is either equally effective or less
 37 effective than ILC. One trial reported that fewer patients were satisfied with
 38 cooling TUMT treatment than with ILC or RFNA.**

39 One RCT (Norby et al. 2002) (N = 94) compared cooling TUMT using the Prostatron 2.0
 40 device to ILC, and reported similar improvements in symptoms, quality of life, and
 41 physiological measures.(129) In a non-randomized trial, Arai et al. (2000) (N = 88)
 42 compared cooling TUMT (using the Dornier Urowave) to interstitial laser coagulation

1 (ILC) and radiofrequency needle ablation (RFNA, or TUNA[®]); ILC appeared to provide
2 more favorable results than TUMT on all reported outcome measures. Results were
3 similar for RFNA and TUMT, although more RFNA patients were satisfied with
4 treatment (55% versus 24%).(130) Significantly more ILC patients than TUMT patients
5 reported being “delighted” or “pleased” (74% versus 24%).(130)

6 Non-Cooling TUMT

7 • **One RCT reported that non-cooling TUMT may improve symptoms but has** 8 **associated adverse events.**

9 One published blinded, multicenter RCT (Albala et al., 2000) (N = 190) compared a non-
10 cooling TUMT device (TherMatrix 2000) to a sham treatment.(177) Non-cooling TUMT
11 improved symptoms more than did sham treatment, but was also accompanied by certain
12 adverse events, including bladder spasm (4.1%), gross hematuria (9.1%), and a need for
13 recatheterization (16.8%patients).(177)

14 • **One RCT reported that non-cooling TUMT and TURP yield similar** 15 **improvements in symptoms and physiological measures, and each has different** 16 **adverse events.**

17 Wagrell et al. (2002)(178) compared non-cooling TUMT to TURP (N = 146).
18 They found that TUMT and TURP provided similar results in all symptom and
19 physiological measures after 12 months. TUMT patients experienced less hematuria
20 (13% versus 39% of patients) and transient incontinence (3% versus 13%) than TURP
21 patients, but more micturition urgency (37% versus 13%) that continued up to 12 months.
22 Catheterization time was longer for TUMT than for TURP (14 versus 3 days), but this is
23 offset by the lack of hospitalization time with TUMT (0 versus 5 days).

24 **Transurethral thermotherapy (TUT)**

25 *Technology Description and Clinical Issues*

26 Thermotherapy is distinguished from hyperthermia by the maximum temperature
27 achieved.(3,183) In thermotherapy treatments, prostate temperatures range from
28 45 degrees to 60 degrees Celsius; in thermotherapy treatments, temperatures range from
29 41 degrees to 44 degrees Celsius. Tissue coagulation is known to occur at temperatures
30 greater than 45 degrees to 50 degrees Celsius, but no clear prostate tissue effects have
31 been demonstrated for temperatures below 45 degrees Celsius.(3)

32 Transurethral thermotherapy appears to be a precursor to the development of
33 transurethral microwave thermotherapy, and was reported on in two controlled trials
34 in 1991.(184,185) No technical details were provided in either trial, and the term
35 “transurethral thermotherapy” has not been used in the published literature since.

36 *Clinical Practice Guidelines*

37 The term “transurethral thermotherapy” is not mentioned in any current clinical practice
38 guideline. The current technology used is transurethral microwave thermotherapy
39 (TUMT), which is covered in a separate section of this report.

1 *Findings*

2 Because this treatment is outdated, we do not further consider the results of controlled
3 trials on it.

4 **Transrectal hyperthermia (TRH)**

5 *Technology Description and Clinical Issues*

6 Hyperthermia is distinguished from thermotherapy by the maximum temperature
7 achieved.(3,183) In hyperthermia treatments, prostate temperatures range from
8 41 degrees to 44 degrees Celsius; in thermotherapy treatments, temperatures range from
9 45 degrees to 60 degrees Celsius. Tissue coagulation is known to occur at temperatures
10 greater than 45 degrees to 50 degrees Celsius, but no clear prostate tissue effects have
11 been demonstrated for temperatures below 45 degrees Celsius.(3)

12 Transrectal microwave hyperthermia (TRH), also called localized deep microwave
13 hyperthermia, uses a rectal applicator to heat prostate tissue to 42 to 44 degrees Celsius.
14 The applicator is connected to a microwave generator (915 MHz, 20-60 W). A cooling
15 system is used to control rectal wall temperature, and a computer system is used for data
16 collection and analysis. Urethral temperature is monitored using a thermosensor
17 contained in a specially designed urethral catheter, and rectal temperature is monitored
18 using a thermosensor in the microwave applicator. During treatment, the maximum
19 prostate temperature is continuously monitored using the rectal and urethral
20 measurements.

21 Transrectal hyperthermia is performed on an outpatient basis and does not require
22 sedation or anesthesia. Treatment lasts approximately 60 minutes and requires multiple
23 sessions, usually once or twice weekly for several weeks. Transrectal hyperthermia is
24 typically delivered in 6 to 10 sessions. However, clinical studies have reported delivery
25 ranging from 3 to 18 treatment sessions.(186-188)

26 Transrectal hyperthermia was under investigation for BPH treatment up to the early to
27 mid 1990s for patients who refused surgery or were at risk for surgical complications.
28 Two controlled trials compared TRH to transurethral thermotherapy,(184,185) while one
29 of these trials also compared it to a prostatic wall stent and prostatic spiral stent.(185)
30 However, no controlled trials were ever published evaluating TRH relative to TURP or
31 any other established treatment method. Although it has applications in treating cancer,
32 transrectal hyperthermia is considered an outdated treatment for BPH.(183)

33 *Clinical Practice Guidelines*

34 Transrectal hyperthermia is not included in any current BPH clinical guidelines. It is
35 therefore not considered further in this evidence report.

36 *Findings*

37 Because this treatment is outdated, we do not further consider the results of controlled
38 trials on it.

1 **Balloon dilation**

2 *Technology Description and Clinical Issues*

3 Balloon dilation for BPH is similar to balloon angioplasty for coronary artery disease.
4 A balloon is inserted into the prostatic channel, guided by a scope or the surgeon's finger,
5 and then inflated. The inflation results in the tearing of prostate gland tissue, which
6 allows passage of urine. Balloon dilation had been considered an alternative to open
7 prostatectomy for the past several years, but has been abandoned because patients often
8 have symptom recurrence and require retreatment within two years. In addition, the
9 procedure is not effective for patients with larger prostate glands.(189)

10 *Clinical Practice Guidelines*

11 In a 1997 guideline, the World Health Organization classified balloon dilation as an
12 unacceptable treatment for BPH.(190) The ICBPH has rated balloon dilation as an
13 unacceptable treatment since 1995.(19) The AUA states that balloon dilation is
14 "not recommended" for treatment of BPH.(3)

15 *Findings*

16 Because this treatment is outdated, we do not further consider the results of controlled
17 trials on it.

18 **Water-induced thermotherapy (WIT)**

19 *Technology Description and Clinical Issues*

20 In WIT, also called balloon thermoablation or liquid ablation, heated water is circulated
21 through a balloon that spans the prostatic urethra. There is a console heating system that
22 heats and maintains water temperature at a chosen temperature between 60 or 70 degrees
23 Celsius, and a peristaltic pump that continuously circulates the water. Usually, WIT
24 protocols use water heated to 60 or 62 degrees Celsius. The circulating water inflates the
25 balloon and conductively heats the prostate tissue, thereby causing coagulation necrosis.
26 During WIT, urethral and rectal temperatures are monitored using temperature sensors.
27 Because the treatment balloon length and catheter length are available in nine lengths,
28 WIT can be used to treat prostates of varying sizes.(191)

29 WIT can be performed on an outpatient basis with local analgesia (lidocaine gel). The
30 procedure takes approximately 45 minutes. In clinical studies, long catheterization times
31 (weeks) or placement of temporary urethral stents were necessary. WIT is not considered
32 an alternative to TURP in patients who can undergo TURP.(191) Rather, it is an option
33 for patients at high risk for surgical complications, such as cardiopulmonary problems, or
34 for patients who may require a less invasive treatment.

35 Although the device (Aquatherm, ACMI; previously Thermoflex, ArgoMed) is FDA-
36 cleared for marketing, WIT is still being researched, since few clinical studies have been
37 published and the protocol (treatment time and temperature) have not been supported by
38 adequate pathologic studies.(192)

1 *Clinical Practice Guidelines*

2 In 2000, WIT was added to the list of interventional therapies evaluated by the ICBPH.
3 The Fifth ICBPH noted that preliminary results of WIT are encouraging, but that further
4 research is needed before clinical acceptance.(19) The AUA considers WIT an “emerging
5 therapy” and states that additional data are required before WIT can be recommended as
6 a treatment option. WIT can be offered to appropriate patients, provided outcomes
7 relative to recommended treatments are discussed with the patient.(3)

8 *Findings*

9 Our searches identified no controlled comparisons of water induced thermotherapy (WIT)
10 to controls or to other treatments.

11 **Transurethral ethanol ablation**

12 *Technology Description and Clinical Issues*

13 Transurethral ethanol ablation, also called absolute ethanol injection, transurethral
14 injection therapy, or chemoablation, involves the injection of absolute alcohol into the
15 prostate lobes. A physician inserts an endoscopic injection device into the urethra via a
16 cystoscope. The needle tip is pushed through the urethral wall into the prostate tissue and
17 alcohol is injected at two to five points, depending on the size of the prostate. The
18 injection induces sclerosis and necrosis of the obstructing prostate tissue.

19 Transurethral ethanol ablation is an outpatient procedure usually performed in about
20 30 minutes with local anesthesia and/or intravenous sedation. Postprocedural
21 catheterization for one to two days is required. Minor side effects include dysuria and
22 hematuria.

23 In 1998 and 2000, endoscopic injection devices received FDA clearance for the injection
24 of biomaterials into the urethra and lower urinary tract. However, the use of absolute
25 alcohol for BPH has not received specific approval and is currently in clinical trials.(193)
26 The AUA considers ethanol treatment an “investigational therapy” and states that it
27 should not be offered outside the context of a clinical trial.(3)

28 *Findings*

29 Our searches identified no controlled comparisons of ethanol ablation to controls or to
30 other treatments.

31 **Prostatic stents**

32 *Technology Description and Clinical Issues*

33 Prostatic stents are spring- or coil-shaped wire devices placed in the prostate channel to
34 keep it open. The stent’s insertion into the prostatic urethra pushes away obstructive
35 tissue. Stents do not normally compete with surgical procedures and all of the less
36 invasive devices, rather stents are typically used for patients who are not candidates for
37 the other procedures and devices. Stent insertion takes approximately 30 minutes under
38 local anesthesia. Thus, stents have been used in patients who cannot tolerate a surgical

1 procedure with general or regional anesthesia due to another medical condition. Stents
2 are most commonly inserted in frail, elderly patients.(194) Problems associated with the
3 use of these stents include irritation and debris accumulation around the stent, stent
4 migration, and increased incidence of urinary tract infections.

5 As of July 2003, one prostatic stent (Urolome™) was FDA approved for marketing for
6 treatment of symptoms secondary to BPH. The approved BPH –related indications are to
7 relieve prostatic obstruction secondary to BPH in men at least 60 years of age, or men
8 less than 60 years of age who are poor surgical candidates, and whose prostates are at
9 least 2.5 cm in length. A contraindication is fracture distraction defects of the posterior
10 urethra. The device is not intended for temporary use.

11 *Clinical Practice Guidelines*

12 The AUA 2003 guidelines suggests that “because prostatic stents are associated with
13 significant complications, such as encrustation, infection and chronic pain, their
14 placement should be considered only in high-risk patients, especially those with urinary
15 retention.”(3) The ICBPH has classified prostatic stents as acceptable with restriction
16 since 1993.(5,19) According to the Fifth ICBPH, prostatic stents have been successfully
17 used in patients at high risk for anesthesia-related complications or who have a short life
18 expectancy, and the ideal patient is frail, elderly, and suffering from urinary
19 retention.(19)

20 *Findings*

- 21 • **One retrospective study reported that fixed stents provide more symptom relief**
22 **and greater improvements in peak urinary flow rates than spiral stents, TUT or**
23 **TRH.**

24 There was one nonrandomized, unblinded, retrospective comparison (Montorsi et al.,
25 1994)(185) among groups of 30 patients who chose a fixed stent (Urolome Wallstent,
26 American Medical System), a spiral stent (Urologische Spirale, Uromed), TUT
27 (Prostatron, Technomed), or TRH (Prostathermer 99D, Biodan Ltd.). All of the patients
28 were poor surgical risks because of previous cerebrovascular accidents, myocardial
29 infarction, coagulation disorders, or obstructive pulmonary disease. Contraindications to
30 these treatments were considered to be a prominent median lobe, prostate or bladder
31 cancer, calculi, neurogenic bladder, or stricture. The patients in the four groups appeared
32 to be fairly well matched in BPH Boyarsky symptom scores and physiological measures.
33 Stents provided better results for symptoms (statistically significant) and slightly better
34 flow rates (not statistically significant) at 12 months. Also, the fixed stent provided
35 significantly better flow rates and symptom scores than the spiral stent. Quality of life,
36 adverse events, perioperative events, and retreatment rates were not reported.

- 1 • **One RCT reported that ILC plus a postoperative stent led to similar**
2 **physiological outcomes and rates of adverse events as ILC alone. This trial**
3 **reported that the addition of the stent allowed resumption of voiding sooner**
4 **after ILC.**

5 A randomized comparison of ILC vs. ILC with stent(195) reported that no differences in
6 physiological outcome measures were observed with or without the stent. Adverse event
7 rates were similarly low for both treatment groups.

8 Use of a stent allowed almost twice as many patients to start voiding on the first day
9 following the operation (81% versus 43%). With the stent, the mean for start of voiding
10 was 1.5 days, compared to over 6 days without the stent (statistically significant).

- 11 • **One trial reported that both a fixed stent and self-expanding stent cause high**
12 **rates of transient irritative symptoms. The authors did not report major**
13 **treatment-efficacy related outcomes.**

14 One trial (randomization not reported) compared a first-generation fixed-caliber stent to a
15 second-generation self-expanding large caliber stent.(196) Short-term irritative symptoms
16 were the primary adverse event experienced by most patients in both the fixed and self-
17 expanding stent groups (80% and 90%, respectively). Correct positioning of the stent was
18 more likely to be achieved in the expanding stent group (100% versus 83% in the fixed
19 group).

20 The authors did not report any outcomes relating to symptoms, physiological measures,
21 quality of life, or retreatment. Lack of data renders it difficult to evaluate the comparative
22 efficacy of these two types of stents.

1 Conclusions

2 Benign prostatic hyperplasia (BPH) primarily affects some middle-aged and very many
 3 elderly men. Consequently, surgical and medical treatments for BPH are some of the
 4 most common therapies administered in all of medical practice. The “gold standard”
 5 treatment for BPH is transurethral resection of the prostate (TURP). In recent years, there
 6 has been a search for less invasive alternatives that will minimize or altogether avoid
 7 some of the undesirable aspects of TURP.

8 A purported advantage of the minimally invasive approach to treating BPH is that such
 9 procedures have fewer side effects compared to TURP. However, the published literature
 10 of controlled trials does not report adverse event rates uniformly and comprehensively
 11 when comparing minimally invasive procedures to TURP. Because some of these
 12 procedures do not appear to be as effective as TURP in relieving symptoms (see bullets,
 13 below), a clear advantage in the incidence of adverse events would be essential in order
 14 to recommend such procedures.

- 15 • Standard surgical alternatives to TURP include transurethral electrovaporization
 16 techniques (TUEVP and TUVRP), open prostatectomy, and transurethral incision
 17 of the prostate (TUIP).
- 18 • Because electrovaporization involves skills and devices similar to those used in
 19 TURP, it can be considered a modification of TURP. Symptoms and peak urinary
 20 flow rates are similar after TUEVP, TUVRP and TURP. Quality of life is also
 21 similar after TUEVP and TURP. Both hospitalization time and catheterization time
 22 are shorter for TUEVP.
- 23 • There are no current direct comparisons of open prostatectomy to TURP. Open
 24 prostatectomy and TURP are now used on different patient populations. Open
 25 prostatectomy is the preferred treatment approach for men with large prostates.
- 26 • TUIP is recommended for men with small prostates. TUIP and TURP provide
 27 similar symptom relief. TUIP results in lower retrograde ejaculation rates and
 28 shorter operation times, as well as shorter catheterization times and hospital stays
 29 than TURP. However, TURP results in higher peak urinary flow rates than TUIP.
- 30 • CLAP and TURP resulted in similar improvements in physiological measures.
 31 CLAP and TURP provided similar symptom relief and similar quality of life
 32 improvements in most trials, but one double-blinded RCT found these outcomes to
 33 be less improved after CLAP than after TURP. CLAP results in less blood loss
 34 than TURP.
- 35 • One year after surgery, symptoms and quality of life improvements are similar
 36 after VLAP and TURP. VLAP requires shorter hospitalizations and longer
 37 catheterization times than TURP. Two trials report that major adverse events are
 38 less likely after VLAP than after TURP. Three trials report that patients who
 39 receive VLAP are more likely to require retreatment than patients who receive
 40 TURP.

- 1 • One controlled trial reported that symptoms and physiological measures improve to
2 a similar degree after HoLAP and TURP. This RCT also reported that HoLAP
3 operations take longer than TURP operations.
- 4 • One trial reported that HoLRP and TURP improve symptoms to a similar degree
5 and that HoLRP operations take longer than TURP operations. However, HoLRP
6 requires a shorter length of stay and catheterization time than TURP.
- 7 • Two trials reported that after six months, HoLEP and open prostatectomy yield
8 similar symptom improvement in patients with large prostates. Two trials reported
9 that HoLEP required shorter hospital stays and one trial reported that HoLEP
10 required shorter catheterization times.
- 11 • ILC and TURP generally provide similar improvements in symptoms and quality
12 of life. Results for physiological measures were mixed. Two trials reported higher
13 retreatment rates after ILC. Unlike TURP, ILC may not require any hospitalization
14 time, but this may be offset by a longer catheterization time.
- 15 • Hybrid laser techniques are too varied to permit general conclusions about this
16 category of treatment for BPH.
- 17 • RFNA results in less symptom and physiological improvement than TURP up to
18 24 months after treatment, and two trials reported that the two treatments have
19 similar effects on quality of life. One trial reported that decreased ejaculate and
20 retrograde ejaculation occur less often after RFNA than after TURP.
- 21 • Only one study examined HIFU, but it was not randomized, and patients in its
22 groups were not comparable.
- 23 • Cooling TUMT leads to improved symptoms and physiological measures up to
24 12 months after treatment. Most trials report that cooling TUMT provides less
25 symptom relief and less improvement in physiological measures than does TURP.
26 One trial reported that retrograde ejaculation was less common after TUMT than
27 after TURP. Retreatment rates may be higher after cooling TUMT than after
28 TURP.
- 29 • One RCT reported that non-cooling TUMT may improve symptoms but has
30 associated adverse events. One RCT reported that non-cooling TUMT and TURP
31 yield similar improvements in symptoms and physiological measures, and each has
32 different adverse events.
- 33 • One retrospective study reported that fixed stents provide more symptom relief and
34 greater improvements in peak urinary flow rates than spiral stents, TUT or TRH.
- 35 • Transrectal hyperthermia, transurethral thermotherapy, balloon dilation, and
36 TULIP are outdated technologies not currently recommended by any professional
37 organization.
- 38 • Ethanol ablations, photoselective vaporization of the prostate and water-induced
39 thermotherapy are emerging therapies not yet studied in controlled trials.

1 The purpose of newer treatments for BPH is to approximate the efficacy of TURP and the
2 other standard surgeries while decreasing the potential harms associated with the standard
3 surgeries. Some of the less invasive treatments do appear to have fewer and/or less severe
4 immediate complications and side effects, and symptom relief approaches that of TURP.
5 Retreatment rates suggest that symptom relief may not be as long lasting as with TURP.
6 However, the published controlled trials are mostly small and short-term, and few of
7 them completely reported the retreatment rates (particularly the need for TURP), adverse
8 events and harms. Long-term effects of these treatments are currently unknown. Hence, it
9 is presently difficult to definitively determine their place within the armamentarium of
10 BPH treatments.

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1 Appendix A: Description of Outcome

2 Measures

3 Trials of treatments for benign prostatic hyperplasia (BPH) examine the effects of
4 treatment on several outcomes. These outcomes may be either beneficial or harmful.
5 Below, we first discuss outcomes that measure potential benefits, and subsequently we
6 describe several potential harms.

7 Potential Benefits

8 There are three categories of benefits of treatments for BPH: symptoms, physiological
9 measures, and quality of life. *Symptoms* and *quality of life* (QoL) are subjective, patient-
10 oriented measures obtained using questionnaires completed by patients, whereas
11 physiological measures are objective measures determined by physicians using
12 systematic instrumented measurements of the functioning of the lower urinary tract.
13 These categories are further defined and described below.

14 The literature on BPH distinguishes between measurements of a patient's *symptoms*, and
15 the degree to which the patient is *bothered* by those symptoms. This is because two
16 patients can have the same level of symptoms, and one patient may be greatly bothered
17 while the other is relatively unbothered. We discuss degree of bother in the section on
18 quality of life.

19 Symptoms

20 Men with BPH experience many symptoms due to enlargement of the prostate. These
21 include a high frequency of urination, pushing or straining during urination, or a painful
22 or burning sensation during urination. To measure symptom severity, clinical trials often
23 use a questionnaire that is completed by the patient. Using a *standardized* questionnaire
24 ensures that different patients are asked precisely the same questions about their
25 symptoms. Further, if different trials use the same questionnaire, then one can compare
26 the degree of symptom improvement across trials. The most commonly used
27 questionnaire is the International Prostate Symptom Score (IPSS)⁵, which appears in
28 Table A- 1.(20) It contains seven questions related to prostate symptoms, and the scores
29 for each question are added to yield a single summary score. The summary score ranges
30 from zero (indicating no symptoms) to 35 (indicating very severe symptoms). A score of
31 seven or less indicates mild symptoms, a score between eight and 19 indicates moderate
32 symptoms, and a score of 20 or higher indicates severe symptoms.(20) Although these
33 cutoff points are arbitrary, a recent review article suggested that this categorization can be
34 used to identify patients with mild symptoms who generally do not require treatment, or
35 to identify patients with severe symptoms for whom treatment is more urgent.(197) The
36 IPSS requires only a sixth-grade reading level,(198) it has been translated into many
37 languages,(197) and it has been recommended for use by the International Consultation

⁵ The IPSS is also known as the American Urologist Association Symptom Score (AUA).

1 on BPH.(199) An estimated 99% of urologists are aware of the IPSS, and 63% use it in
2 clinical practice.(199)

3 In addition to the IPSS, several other BPH symptom questionnaires have been developed
4 (Table A- 2). All of these questionnaires contain questions similar to those in the IPSS
5 (e.g., nighttime frequency of urination, weak urinary flow, incomplete emptying of the
6 bladder). Some pose questions not in the IPSS, such as questions about hesitancy before
7 urination and post-urinary dribbling. All of the questionnaires employ slightly different
8 wording and use different response scales that could potentially influence patients'
9 scores. However, the correlations between questionnaires are all high (published
10 correlations range from 0.51 to 0.93),(200,201) indicating that they measure similar
11 aspects of patients' BPH symptoms.(200)

12 All of the symptom questionnaires rely on patients' memories of their recent symptoms.
13 Because memories are imperfect, it is important to assess both the *validity* and *reliability*
14 of symptom questionnaires. Validity refers to whether a questionnaire measures what it is
15 intended to measure. In the present context, there is no "gold standard" for the patient's
16 true symptoms, so one cannot assess validity in the strictest sense. Consequently,
17 researchers have attempted to assess validity indirectly (specifically, "construct" validity)
18 by determining whether patients' scores on a symptom questionnaire correlate well with
19 other relevant measures, such as whether patients report global improvement after
20 treatment. If they do, then the questionnaire is said to have construct validity. This has
21 been established for three of the questionnaires listed in Table A- 2. The IPSS correlates
22 well with the degree to which patients were bothered by their symptoms,(20) patient
23 global ratings of improvement after treatment,(202) and global ratings of bother.(20)
24 The Dan-PSS(203) and the ICSmaleSF(204) also correlate well with these measures.

25 Reliability refers to the repeatability of a questionnaire. Two types of reliability are
26 usually investigated: *test/retest reliability* and *internal consistency*. Test-retest reliability
27 concerns whether the same patient gives the same answers at different times. For
28 example, a patient could complete a symptom questionnaire on March 1st, and then
29 complete it again on April 1st. If the patient gives the same responses, then the test has
30 good test-retest reliability (assuming there was no treatment intervention during the
31 month of March). Internal consistency addresses whether responses to individual
32 questions in the questionnaire are correlated, and if so, they are believed to measure the
33 same underlying construct. Empirical trials have found good test-retest reliability
34 (Pearson r 0.8-0.9) and good internal consistency reliability (Cronbach's alpha 0.7-0.8)
35 for three symptom questionnaires (the same three for which validity has been
36 established): the IPSS,(20) the Dan-PSS,(203) and the ICSmaleSF.(204)

37 Despite the fact that these questionnaires are reliable and valid, there are challenges to
38 using them to measure the effect of treatment. This is because patients generally expect to
39 improve after treatment. Thus, they may report fewer symptoms after treatment even if
40 there was no real improvement.(24) This possibility is strong motivation for the use of a
41 blinded control group in any trial of BPH treatment. Patients in both groups (the
42 treatment group and the control group) might expect to improve, thus any comparison
43 between groups must factor out any effect of patients' expectations.

1 Ideally, patients in the control group would receive a placebo, because the placebo effect
 2 is a well-established finding in BPH research. In a review of 1,417 patients in 45 placebo
 3 arms of BPH clinical trials, Roehrborn (1996)(205) found that 42% of placebo-treated
 4 patients experienced an improvement in their symptoms after “treatment.” In addition,
 5 the review noted that the Food and Drug Administration and the World Health
 6 Organization “advocate rather strictly the use of placebo controls” (p 242) in the field of
 7 BPH research.(205)

8 Expectation is less likely to affect more objective outcome measures, such as the
 9 physiological measures described in the next section. However, as discussed below, these
 10 physiological measures are an indirect way to measure the most important outcomes of
 11 treatments for BPH.

Table A- 1. International Prostate Symptom Score (IPSS)

Question	Not at All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Quality of life question (IPSS QOL)						
	None	1 Time	2 Times	3 Times	4 Times	5 + Times
Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

12 The scores for each question are added to yield the summary symptom score, which ranges from
 13 0 (indicating no symptoms) to 35 (indicating very severe symptoms).(20)

1 **Table A- 2. Symptom Questionnaires**

Questionnaire	Primary reference	Number of questions	Validity?	Reliability?
Boyarsky ^a	Boyarsky et al. (1977)(206)	9		
Madsen and Iversen	Madsen and Iversen (1983)(21)	9		
IPSS (AUA) ^b	Barry et al. (1992)(20)	7	✓	✓
Dan-PSS	Hansen et al. (1995)(203)	12	✓	✓
ICSmaleSF	Donovan et al. (2000)(207)	11	✓	✓

2 IPSS - International Prostate Symptom Score (also called the American Urologist Association Symptom
3 Score)

4 Dan-PSS - Danish Prostatic Symptom Score

5 ICSmaleSF - International Continence Society Symptom Frequency for males

6 a Bolognese(208) proposed a slight alteration of the Boyarsky scale, thus it is not listed in the table.

7 b The Maine Medical Assessment Program questionnaire(209) was an early version of the IPSS, thus it is
8 not listed in the table

9 ✓ - Indicates that reliability or validity have been tested and confirmed (see explanation in text)

10 **Physiological measures**

11 BPH involves an enlargement of the prostate that decreases bladder capacity and restricts
12 the flow of urine. Thus, physiological measures such as prostate size, speed of urine flow,
13 and pressure on the urethra are reported in trials of treatments for BPH. The commonly
14 reported physiological measures are listed and described in Table A-3.

15 Physiological measures are relevant because they are objective measures of physiological
16 causes of the symptoms of BPH. If these measures really do reflect the causes of the
17 symptoms, then one would expect high correlations between physiological measures and
18 symptom scores. Several trials have investigated such correlations, and all have
19 concluded that they are low.(210-213) For example, a 1995 trial by Bosch, Hop,
20 Kirkels et al.(212) found only a small correlation (Spearman $r = 0.19$) between symptom
21 scores on the IPSS and prostate volume (a list of the published correlations appears in
22 Table A-4). This suggests that, on average, there is a slight tendency for men with more
23 symptoms to have larger prostates. However, it also suggests that there were some men
24 with mild symptoms and large prostates, and there were other men with severe symptoms
25 but small prostates. Consequently, prostate size itself does not adequately explain why
26 some men have mild symptoms and others have severe symptoms.

27 Given the absence of strong correlations between symptoms and physiological measures,
28 which outcome category is more important in assessing the efficacy of treatments for
29 BPH? Symptom scores are more patient-oriented: a patient cares more about his
30 symptoms than the actual speed of urinary flow or the size of his prostate. The
31 physiological measures, therefore, are indirect measures of what matters to patients.

1 Thus, in the face of a discrepancy between symptom scores and physiological measures,
2 a patient-oriented analysis would emphasize the symptom scores. However, symptom
3 scores are vulnerable to expectation effects, whereas physiological measures are
4 relatively free from such effects. Expectation effects on symptom scores motivate the
5 need for blinded control groups in BPH treatment trials, because the expectation effects
6 would be cancelled out in any between-groups comparison.

7 Although physiological measures are less susceptible to placebo effects than are
8 symptom scores, they are still susceptible to a statistical artifact called *regression to the*
9 *mean*.(24) Symptoms of BPH fluctuate over time,(214,215) and patients tend to be
10 recruited into trials when they are relatively sick (i.e., when they meet stringent inclusion
11 criteria).(24) An observed “improvement”, therefore, may simply reflect a return to the
12 patient’s typical level of health.⁶ For example, a patient could be recruited into a trial
13 when he had a relatively slow urinary flow rate (a physiological measure). During the
14 trial, the patient’s flow rate could be faster, not because of the treatment, but instead
15 because the trial observed a more typical flow rate for that patient (i.e., closer to that
16 patient’s mean). Regression to the mean provides further motivation for the use of a
17 control group in any clinical trial of BPH. Patients in different groups but the same
18 selection criteria would likely experience the same amount of regression to the mean,
19 so the between-groups comparison would not be confounded.

⁶ The “improvement” could also be due to a placebo effect. Both of these possibilities (regression-to-the-mean and a placebo effect) are contrary to the claim that the improvement was actually caused by the treatment. For a detailed discussion of this point, see Sech, Montoya, Bernier et al. (1998).(24)

1 **Table A- 3. Physiological measures**

Measure (abbreviation)	Description
Peak urinary flow rate (Q_{max})	During urination, the maximum amount of urine expelled per minute (measured in liters per minute or milliliters per minute). Higher values indicate better outcomes.
Voided volume	The amount of urine expelled during urination (measured in liters or milliliters). Higher values indicate better outcomes.
Postvoid Residual Volume (PVR)	After urination, the amount of urine remaining in the bladder (measured in liters or milliliters). Lower values indicate better outcomes.
Relative Residual Volume	The percentage of urine remaining in the bladder after urination. Lower values indicate better outcomes.
Prostate volume	Size of the prostate (measured in cubic centimeters). Lower values indicate better outcomes.
Detrusor pressure at peak urinary flow	During urination, the amount of pressure on the urethra (measured in number of centimeters water) at the time of peak urinary flow. Lower values indicate better outcomes.
Urethral resistance factor	During urination, the amount of pressure on the urethra (measured in number of centimeters water) at zero flow rate, interpolated from a plot of flow rate and pressure. See Bosch(216) for details. Lower values indicate better outcomes.
Minimal urethral opening pressure	During urination, the minimum amount of pressure on the urethra (measured in number of centimeters water) at the beginning of urination, interpolated from a plot of flow rate and pressure. See Bosch(216) for details. Lower values indicate better outcomes.
Prostate specific antigen (PSA)	An antigen in the blood that is released by the prostate (measured in nanograms per milliliter). Lower levels of this antigen indicate better outcomes.

2

1 **Table A- 4. Correlations between physiological measures and**
 2 **symptom scores**

Physiological measure	Correlation with symptom scores ^a
Maximum flow rate (Q_{max}) ^b	-0.07(210)
	-0.12(211)
	-0.18(212)
	-0.24(213)
Average flow rate	-0.13(210)
	-0.25(213)
Postvoid residual volume (PVR)	0.01(210)
	0.05(211)
	0.25(212)
Relative residual volume	0.10(211)
Voided volume	-0.21(213)
Total prostate volume ^c	-0.09(210)
	0.03(211)
	0.19(212)
Central prostate volume ^d	0.24(212)
Prostate specific antigen (PSA)	-0.06(210)
Obstruction grade ^e	0.02(211)

3 ^a Symptom score as measured by the International Prostate Symptom Score (IPSS)

4 ^b Donovan, Abrams, Peters et al. (1996)(204) also found a weak relation between maximum flow rate and
 5 symptom scores, but they did not report the value of the correlation.

6 ^c Simpson, Fisher, Lee et al. (1996)(213) computed the correlation between total prostate volume and
 7 symptom scores, and found “no statistically significant relation”, but they did not report the value of the
 8 correlation.

9 ^d Volume of the central part of the prostate.

10 ^e Obstruction grade is an urodynamic parameter derived from the minimal urethral opening pressure.(211)

11 **Quality of life**

12 Some trials report how treatments of BPH affect patients’ overall quality of life (QOL).
 13 This is a more general outcome measure than symptoms, physiological measures, or
 14 adverse events, because QOL can incorporate cognitive abilities, activities of daily living,
 15 and family relationships. With regard to BPH, QOL measures can assess the
 16 *bothersomeness* of a patient’s symptoms. Two patients can have identical symptoms, but
 17 one patient may be greatly bothered by those symptoms and the other patient relatively
 18 unbothered.

19 Quality of life questionnaires can be grouped into two categories: *disease-specific* and
 20 *generic*. Disease-specific questionnaires only contain questions about how BPH itself
 21 affects quality of life. For example, one disease-specific question is: “If you were to
 22 spend the rest of your life with your prostate symptoms just as they are now, how would
 23 you feel about that?”(20) Patients respond on a 0-6 scale where 0 means “delighted” and
 24 6 means “terrible.” By contrast, a generic QOL questionnaire does not refer to any
 25 particular disease, but instead contains questions about the patients’ QOL in general.

1 For example, one question in the Short Form 36 (SF-36) asks: “During the past 4 weeks,
 2 how much did pain interfere with your normal work (including work both outside the
 3 home and housework)?”(217) Patients respond on a 0-4 scale where 0 means “not at all”
 4 and 4 means “extremely.” Disease-specific questionnaires are more sensitive than generic
 5 questionnaires to BPH treatment effects.(218-220)

6 A list of the QOL questionnaires that have been used to assess BPH treatments appears in
 7 Table A- 5. Some questionnaires consist of only one question,(20,207) whereas one
 8 contains 44 questions.(221) As with the symptom questionnaires discussed earlier, all of
 9 these questionnaires are vulnerable to expectation effects, and the use of blinded control
 10 groups can address this difficulty.

11 **Table A- 5. Quality of life questionnaires**

Disease-specific quality of life questionnaires		
	Number of questions	Description
BPH Impact Index	4	Questions about the bothersomeness of specific BPH symptoms, including physical discomfort, worry, trouble with urination, and prevention of normal activities. Summary score ranges from 0 to 13 where 0 indicates no bother and 13 indicates extreme bother.(202)
Global question ^a	1	“If you were to spend the rest of your life with your prostate symptoms just as they are now, how would you feel about that?” (0 = Delighted, 1 = Pleased, 2 = Mostly satisfied, 3 = Mixed, 4 = Mostly dissatisfied, 5 = Unhappy, 6 = Terrible)(20)
Bothersomeness questions in Dan-PSS	12	Questions about the bothersomeness of specific BPH symptoms. Each question corresponds to a symptom question in the Dan-PSS.(203) The summary score for bother ranges from 0 to 36 where 0 indicates no bother and 36 indicates extreme bother.
ICSQoL single question ^b	1	“Overall, how much do your urinary symptoms interfere with your life?” (0 = not at all, 1 = a little, 2 = somewhat, 3 = a lot)(207)
ICSQoL	6	Questions about bothersomeness of symptoms and interference with daily life.(222)
QOL9	9	Ratings from 0-10 for each of nine domains. Minimum score is 0, maximum score is 90.(223)
Epstein	44	Questions in each of six domains. Minimum score is 0, maximum score is 239.(221)
Generic quality of life questionnaires		
Short Form-36 (SF-36)	36	Questions in each of eight domains: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions.(217,224-227)
EuroQOL	14	Questions in each of six domains: mobility, self-care, usual activities, pain/discomfort, mood, and general health.(228,229)
Psychological General Well Being	22	Questions in each of five domains: depression, anxiety, self-control, vitality, and positive attitude.(230,231)
Nottingham Health Profile	38	Questions in each of six domains: energy level, pain, emotional reaction, sleep, physical mobility, and social isolation.(228,232)

Functional Living Index - Cancer	22	Questions related to social support, activities of daily living and other domains.(233,234)
Rand Mental Health Index-17	17	Questions in five domains of psychological distress and well-being: anxiety, depression, behavioral-emotional control, belonging/loneliness, and positive affect.(233,235)

- 1 ^a This is an optional add-on to the International Prostate Symptom Score (IPSS).
- 2 ^b This is an optional add-on to the International Continence Society Symptom Frequency for males (ICSmaleSF).
- 3 SF-36 Short Form 36
- 4 Dan-PSS Danish Prostatic Symptom Score
- 5 EuroQOL-5D European quality of life questionnaire, version 5D

6 **Potential Harms**

7 Treatments can have harms as well as benefits. In this section, we discuss three categories
 8 of potential harms that can be caused by treatments for BPH: perioperative outcomes,
 9 adverse events and retreatment. *Perioperative* outcomes occur during the operation (or
 10 soon after), *adverse events* can occur soon after the operation or after a delay, and
 11 *retreatment* involves the long-term question of whether a treatment ultimately results in
 12 the need for additional treatment (due to the lack of benefit or declining benefit). These
 13 outcomes are further addressed in the Results sections of this report.

14 **Perioperative outcomes**

15 Patients receiving certain surgical treatments can require transfusions. Thus, trials often
 16 report the number of patients who required transfusions, the amount of blood loss, and
 17 the amount of blood that was transfused. Additional intraoperative measures included
 18 operation time, anesthesia usage, and the amount of prostate tissue resected. Immediately
 19 after the operation, most treatments for BPH require urethral catheterization, so many
 20 trials report the number of days that patients were catheterized as well as the length of
 21 hospitalization. Some trials also report postoperative changes in serum levels of
 22 hemoglobin, hematocrit, sodium, or other variables that are affected by the mixing of
 23 irrigation fluids with the patients’ blood during the operation.

24 **Adverse events**

25 All treatments for BPH are associated with some adverse events. For any treatment
 26 decision, one should consider both the frequency and the severity of adverse events.
 27 These are weighed against the potential benefits of a treatment. The choice between
 28 treatments involves a tradeoff between efficacy and adverse events, in which a treatment
 29 with greater efficacy, but more potential adverse events, is compared to an alternative
 30 treatment with lower efficacy, but fewer adverse events.

31 Some events are experienced soon after treatment, whereas others are experienced after a
 32 few weeks or months. The commonly reported adverse events of treatments for BPH are
 33 listed and described in Table A- 6. Additional potential adverse events include mortality,
 34 myocardial infarction, stroke, deep venous thrombosis, fever, impaired ejaculation, and
 35 decreased libido. Surgical techniques (such as transurethral resection of the prostate, or
 36 TURP) are associated with different categories of adverse events than non-surgical
 37 techniques (such as transurethral microwave thermotherapy, or TUMT). For example,

1 some patients experience blood loss requiring transfusion after TURP, but none
 2 experience it after TUMT.(6)

3 **Table A- 6. Adverse events**

Adverse event	Description
Bladder neck contracture	Shortening of muscle tissue in the bladder neck
Dilutional hyponatremia	Inadequate sodium in the blood
Dysuria	Pain (burning sensation) or difficulty in urination
Impotence	Inability to achieve or maintain an erection
Retrograde ejaculation	Ejaculation in which semen travels backwards towards the bladder
Urinary retention	Inability to initiate urination
Urethral stricture (stenosis)	Narrowing or closing of the urethra
Urinary incontinence	Inability to control the flow of urine, resulting in dribbling.
Urinary tract infection (UTI)	Infection of the urinary tract

4 **Retreatment**

5 For some patients with BPH, the original treatment does not relieve symptoms or the
 6 relief is temporary, and it is necessary to retreat the patient. This provides evidence
 7 against the efficacy of the original treatment. If the original treatment had worked, then
 8 retreatment would not be necessary. The retreatment can be a repetition of the original
 9 treatment, or it can be a different treatment altogether. If one wishes to compare any two
 10 treatments, an important consideration is which treatment is associated with a lower
 11 (i.e., better) rate of retreatment. A related issue is which treatment is associated with a
 12 greater amount of time before retreatment.

13 Several reviews have argued that retreatment is a useful outcome measure in treatments
 14 for BPH.(6,236-238) It is an objective measure of a patient-oriented outcome. Patients
 15 care about the need for retreatment because they must endure the persistence of
 16 symptoms as well as any adverse events caused by the retreatment.

17 Despite compelling reasons for measuring retreatment, many trials do not report it.
 18 One possible reason for this is the need for sufficient followup time. If a trial has a short
 19 followup period, then it is less able to detect patients who require retreatment.

20 Even if a trial has long-term followup, there may still be difficulties with comparing
 21 retreatment rates between treatments. One difficulty concerns patient selection bias.
 22 If the patients who received one treatment were systematically different from patients
 23 who received the other treatment (e.g., they had more severe symptoms before treatment),
 24 then a simple comparison of retreatment rates would be biased. This difficulty can be
 25 addressed by randomly assigning patients to treatments. Another difficulty is that
 26 treatment failure does not necessarily imply the need for retreatment. Some patients may
 27 experience the failure of a treatment, but their symptoms are not severe enough to justify
 28 retreatment.

1 Appendix B: Description of Utilities

2 This section focuses on patients’ reactions to the outcomes of BPH treatments (or more
3 specifically, “utilities”, described in detail below). We first provide background
4 information on what utilities are and how they are measured. Then, we review the
5 evidence on patients’ utilities for the outcomes of treatments for BPH.

6 Background on utilities

7 The word “utility” in medical decision making refers to the relative amount of value or
8 worth that a patient places on a given outcome.⁷ Utility is measured on a scale from 0 to 1
9 where 0 indicates the lowest possible utility and 1 indicates the highest possible utility.
10 Suppose a patient is asked how he would feel if he had severe incontinence. If a patient
11 places a relatively low utility (such as 0.25) on this health state, then this means that he
12 perceives it quite negatively. Alternatively, if the patient assigns a relatively high utility
13 to this health state (e.g., 0.85), then he does not think it would be so bad. Using utilities,
14 a patient can express his opinions about the relative values of different outcomes. The
15 concept of utility has been used in a medical decision analysis of BPH treatments to
16 compare the overall desirability of different treatments.(239) Also, utilities have been
17 employed in cost-effectiveness analyses⁸ of BPH treatments.(22,240-242)

18 Utilities can be measured in several ways. Here, we describe two methods for measuring
19 utilities: the time tradeoff (TTO) and the standard gamble (SG). The time tradeoff method
20 (TTO) presents patients with a series of hypothetical choices. By asking the patient to
21 state his preferences between hypothetical alternatives, the researcher can determine the
22 degree of subjective value or worth that the patient places on an outcome. The central
23 issue is how many years of life the patient is willing to give up in order to avoid living
24 with a debilitating health state. If a patient perceives the health state as being extremely
25 poor, then he may be willing to live a shorter life if it means he could avoid the
26 debilitating health state. For example, to determine a patient’s TTO utility for severe
27 incontinence, a researcher would first ask the patient to choose between the following
28 two hypothetical alternatives:

29 *Alternative A:* You live for the next 10 years with severe incontinence, after which you
30 would die painlessly.

31 *Alternative B:* You live for the next 9 years in perfect health (i.e., no symptoms of BPH),
32 after which you would die painlessly.

⁷ The concept of utility was introduced by economists to explain why different people perceive the value of money differently. Researchers have applied utilities to medical decision analysis by computing an “expected utility” for each treatment, and the treatment with the highest expected utility is preferred. An introduction to this topic appears in a book by Sox, Blatt, Higgins, et al. (1988).(245) Utilities are also used as quality weights in quality-adjusted life years (“QALYs”) as a way to compare treatments for their combined effects on quality and quantity of life.(264)

⁸ A cost-effectiveness analysis that uses utilities to measure effectiveness is also referred to as a “cost-utility” analysis.

1 Some patients may be willing to give up a year of life in order avoid severe incontinence,
2 but other patients may not be willing. If the patient prefers Alternative A, then the
3 researcher presents another hypothetical choice in which Alternative B is made more
4 attractive by increasing the number of years in perfect health (e.g., to 9.5 years).⁹ The
5 patient is then asked to choose between these new Alternatives A and B. The process
6 continues until the patient is *indifferent* between the two alternatives (i.e., A and B are
7 equally preferable). The point of indifference determines the patient's utility. For
8 example, suppose the patient is indifferent between Alternatives A and B when
9 Alternative B is 8.5 years in perfect health. This would mean that the patient's TTO
10 utility for severe incontinence is 8.5/10 or 0.85.

11 Like the TTO, the standard gamble method (SG) requires patients to make choices
12 between hypothetical alternatives. Unlike the TTO, however, the SG uses the concept of
13 risk. For example, suppose one wants to determine a patient's SG utility for severe
14 incontinence. To measure this utility, Ackerman, Rein, Blute, et al. (2000)(22) asked
15 patients with BPH to choose between the following hypothetical alternatives:

16 Alternative A: Severe incontinence. You have undergone treatment for BPH that results
17 in a total loss of voluntary control over urination.

18 Alternative B: A gamble in which there is a 90% chance of having perfect health (i.e., no
19 BPH symptoms and no adverse events), but there is a 10% chance of death.

20 If the patient prefers Alternative A, then Alternative B is made more attractive by
21 increasing the chance of perfect health (e.g., to 95%) and decreasing the chance of death
22 (e.g., to 5%),¹⁰ and the patient is asked to choose between these new Alternatives A and
23 B. As with the TTO, the process continues until the patient is indifferent between the two
24 alternatives. The point of indifference determines the patient's utility. For example,
25 suppose the patient is indifferent between Alternatives A and B when Alternative B is a
26 95% chance of perfect health and a 5% chance of death. This would mean that the
27 patient's utility for severe incontinence is 95/100 or 0.95.

28 The two methods approach the problem differently, and they can produce different
29 results.(243) The SG (but not the TTO) incorporates patient's attitudes towards risk, and
30 because patients tend to be averse to risks,(244) the SG is assumed to be as the "gold
31 standard" for utility measurement.(245)

32 One difficulty with utility measurement concerns the hypothetical nature of the elicitation
33 process. Both methods require the patient to *imagine* what it would be like to live in a
34 specific health state. The patient's responses are based, therefore, on his imagined
35 response to this health state, which may be different from his true response to the health
36 state if he actually experienced it. However, this difficulty is not unique to utility

⁹ If the patient prefers Alternative B, then Alternative B is made less attractive by decreasing the number of years in perfect health (e.g., to 8.5 years). The process continues until the patient is indifferent between the alternatives.

¹⁰ If the patient prefers Alternative B, then Alternative B is made less attractive by decreasing the chance of perfect health (e.g., to 85%) and increasing the chance of death (e.g., to 15%). The process continues until the patient is indifferent between the alternatives.

1 measurement. In any medical treatment, outcomes may occur that the patient has never
2 experienced, and the patient's reaction to those outcomes cannot be known in advance.

3 A more fundamental difficulty with utility measurement concerns the quantifiability of
4 patient's values. Both methods attempt to assign a number to a patient's opinion about a
5 health state. This number may depend on many unintended factors, such as the way the
6 health state is described(246) or the manner in which the choice is framed.(247) Also, a
7 patient's opinion can change over time, suggesting that no single number can fully
8 capture his beliefs about a health state.(248) With these caveats in mind, the next section
9 reviews the available evidence on patients' utilities for the outcomes of BPH treatments.

10 **Evidence on utilities for BPH**

11 Only two studies have reported BPH patients' utilities (in their technical sense) for
12 treatment outcomes.¹¹ Ackerman et al. (2000)(22) used the standard gamble to measure
13 the preferences of 13 men with moderate to severe symptoms of BPH.¹² They reported
14 the mean SG utilities for five short-term events and 17 long-term outcomes of BPH
15 treatments. According to the mean SG utilities, patients perceive myocardial infarction as
16 the worst among the five short-term events, followed by deep venous thrombosis. Among
17 the long-term outcomes, patients perceived severe incontinence as the worst, followed by
18 urinary retention. These utilities, which were 0.80 and 0.82, respectively, show that
19 patients perceive these outcomes rather negatively. Also, note that there were three
20 categories of remission: no remission, moderate remission, and significant remission.
21 Within each of these categories, there was a consistent ordering of three adverse events:
22 erectile dysfunction, urinary incontinence, and ejaculatory dysfunction. Specifically, the
23 typical patient thought erectile dysfunction was worse than urinary incontinence, which
24 was perceived to be worse than ejaculatory dysfunction.

25 Schulz et al. (2002)(23) used the time tradeoff (TTO) technique to measure utilities. They
26 enrolled 29 patients with a mean I-PSS symptom score of 16.2, indicating that the typical
27 patient had moderate LUTS. Each patient performed the time tradeoff task for each of
28 two health states (current level of symptoms, and the worst possible level of symptoms)
29 at each of two time intervals (1 year and 10 years). The mean TTO utilities (and ranges)
30 appear in Table B- 2. The typical patient was willing to give up 14%-20% of time in
31 order to relieve their current symptoms. When presented with a hypothetical situation
32 involving the worst possible BPH symptoms,¹³ the typical patient was willing to give up
33 46%-52% of time in order to avoid that scenario.

34 In summary, one study used the standard gamble method, whereas the other used the time
35 tradeoff method. The study by Ackerman et al. (2000)(22) showed that the typical patient

¹¹ Two additional studies addressed similar issues, but they are not discussed here for the following reasons. Krumins, Fihn and Kent (1988)(265) employed the time tradeoff (TTO) technique to measure the utilities of men with BPH, but they did not report summary statistics on the measured TTO utilities. Llewellyn-Thomas et al. (1996)(266) reported SG utilities of a group of men who were seen at a urology clinic for an initial diagnostic assessment for BPH, and some of them may not have had BPH.

¹² As measured by I-PSS symptom scores between 15 and 29, inclusive.

¹³ As defined by an I-PSS score of 35, which is the maximum on this instrument.

1 was willing to risk death in order to avoid potential short term adverse events (such as
2 myocardial infarction) and long-term outcomes (such as severe incontinence). The study
3 by Schulz et al. (2002)(23) found that the typical patient was willing to give up some of
4 their lifespan in order to cure their current symptoms of BPH. Jointly, the studies indicate
5 a clear desire on the part of patients both to cure their symptoms and to avoid adverse
6 events. However, because there were only two studies, the findings prevent firm
7 conclusions about patients' precise values.

1 **Table B- 1. Mean standard gamble utilities in Ackerman et al. (2000)**

Short-term events	Mean SG utility¹	Range
Myocardial infarction	0.78	0.69 - 0.95
Deep venous thrombosis	0.89	0.74 - 0.99
Severe urinary tract infection	0.93	0.77 - 0.99
Urethral stricture/bladder neck contracture	0.94	0.78 - 1
Dysuria	0.97	0.83 - 1
Long-term outcomes²	Mean SG utility	Range
Severe incontinence	0.8	0.5 - 0.98
Urinary retention	0.82	0.5 - 1
Worsening BPH and ejaculatory dysfunction	0.9	0.78 - 1
Worsening BPH and no adverse events	0.92	0.78 - 1
No remission and erectile dysfunction	0.9	0.78 - 1
No remission and urinary incontinence	0.93	0.82 - 1
No remission and ejaculatory dysfunction	0.95	0.78 - 1
No remission and no adverse events	0.96	0.83 - 1
Moderate remission and erectile dysfunction	0.92	0.83 - 1
Moderate remission and urinary incontinence	0.94	0.82 - 1
Moderate remission and ejaculatory dysfunction	0.96	0.84 - 1
Moderate remission and no adverse events	0.98	0.92 - 1
Significant remission and erectile dysfunction	0.93	0.83 - 1
Significant remission and urinary incontinence	0.95	0.84 - 1
Significant remission and ejaculatory dysfunction	0.97	0.84 - 1
Significant remission and no adverse events	1	0.94 - 1

2 ¹ These means were calculated by ECRI based on the means provided in Table I on page 975 of Ackerman,
 3 Rein, Blute, et al. (2000).(22) Values were rounded to the nearest 0.01.

4 ² An additional long-term outcome was “moderate-to-severe BPH,” which was identical to the outcome
 5 “No remission and no adverse events”, thus it is not listed separately in the table. This outcome
 6 corresponds to *no* effect of the treatment (i.e., no benefit and no harm). The authors also reported utilities
 7 for three treatments for BPH, but these are not listed in the table because this section addresses the
 8 utilities for potential *outcomes* of treatments, not utilities for the treatments *per se*.

9 SG - Standard gamble utility (see explanation in text).

1 **Table B- 2. Mean time tradeoff utilities in Schulz et al. (2002)**

Health state	Time interval ¹	Mean TTO utility	Range
Current level of symptoms	1	0.86	0.13-1
Current level of symptoms	10	0.80	0.05-1
Worst possible level of symptoms ²	1	0.54	0.04-1
Worst possible level of symptoms ²	10	0.48	0.05-1

2 ¹ The time interval refers to the time that the patient would spend in the corresponding health state.
 3 For example, in the first row, the typical patient was indifferent between living for 1 year with current
 4 symptoms and living for 0.86 years in perfect health. The second row indicates that the typical patient was
 5 indifferent between living for 10 years with current symptoms and living for 8 years (0.80 x 10) in perfect
 6 health.

7 ² The worst possible level of symptoms was defined as an I-PSS score of 35, which is the highest (worst)
 8 possible score on that instrument.

9 TTO Time tradeoff (see explanation in text).

10

1 **Appendix C: Literature Search Strategies**

2 **Electronic Database Searches**

3 We searched the following databases for relevant information:

4 Cochrane Database of Systematic Reviews (through 2003, Issue 2)

5 Cochrane Registry of Clinical Trials (through 2003, Issue 2)

6 Cochrane Review Methodology Database (through 2003, Issue 2)

7 Database of Reviews of Effectiveness (Cochrane Library) (through 2003, Issue 2)

8 ECRI Health Technology Trends (through December 2002)

9 ECRI International Health Technology Assessment (IHTA) (1991 through January 2003)

10 ECRI Library Catalog (through January 2003)

11 ECRI TARGET (through January 2003)

12 Embase (Excerpta Medica) (1991 through December 26, 2002)

13 PsycINFO (1989 through December 26, 2002)

14 PubMed (MEDLINE, PreMEDLINE, HealthSTAR) (1975 through November 14, 2003)

15 TRIP Database (through December 5, 2002)

16 U.K. National Health Service Economic Evaluation Database (NHS EED)

17 (through January 2003)

18 U.K. National Institute for Clinical Excellence (NICE) (through December 17, 2002)

19 U.S. National Guideline Clearinghouse™ (NGC™) (through January 2003)

20 **PubMed searches**

21 For PubMed, the following strategy was used to limit results to controlled clinical trials:

22 Controlled clinical trials:

23 (randomized controlled trials(164) OR random allocation(164) OR randomized controlled
24 trial(8) OR double-blind method(164) OR single-blind method(164) OR “single-dummy”
25 OR “double-dummy” OR controlled clinical trials(164) OR controlled clinical trial(8) OR
26 placebo* OR controls[ab] OR “latin square”[tw])

27 All searches were limited to English language publications and human population.

28 The following strategy was used for these limits:

29 English[la] AND (human(164) OR premedline(222) OR publisher(222))

- 1 Benign Prostatic Hyperplasia (BPH):
- 2 1) prostatic hyperplasia(164)
 - 3 2) “bph” OR “benign prostatic hyperplasia”
 - 4 3) (benign OR enlarg* OR hyperplasia OR hypertroph*) AND prostat*
 - 5 4) “bladder outlet obstruction” AND (male(164) OR prostate OR prostatic)
 - 6 5) #1 OR #2 OR #3 OR #4
 - 7 6) #5 NOT (adenoma* OR adenocarcinoma* OR neoplasms(164))
 - 8 7) #5 NOT #6
 - 9 8) #7 AND #2
 - 10 9) #6 OR #8
- 11 Therapies for BPH:
- 12 Alcohol ablation of the prostate:
- 13 1) #9 AND (injections, intralesional(164) OR “chemo-ablation” OR
 - 14 chemoablation)
 - 15 2) #9 AND (ethanol OR alcohol) AND (inject OR injection)
 - 16 3) #9 AND sclerotherapy
 - 17 4) #1 OR #2 OR #3
- 18 Balloon dilatation of the prostate (BDP):
- 19 1) #9 AND (balloon dilatation(164) OR (balloon AND dilat*) OR “BDP”)
- 20 Cryotherapy:
- 21 1) #9 AND (cryotherapy OR cryotherapeutic OR cryosurgery OR cryosurgical
 - 22 OR hypotherm*)
- 23 High-intensity focused ultrasound (HIFU):
- 24 1) #9 AND (ultrasonic therapy OR ultrasound OR ultrasonic) AND (transrectal
 - 25 OR rectal OR endorectal)
 - 26 2) #9 AND (“high-intensity focus ultrasound” OR “HIFU”)
 - 27 3) #9 AND sonoblate
 - 28 4) #1 OR #2 OR #3
 - 29 5) #4 AND (therapeutic use[sh] OR therapy[sh] OR publisher(222) OR
 - 30 premedline(222))
- 31 Laser surgery:
- 32 1) #9 AND (laser surgery(164) OR (laser AND (ablation OR interstitial OR
 - 33 holmium OR Endoscopic)) OR ELAP OR VLAP OR HoLEP OR HOLEP)
- 34 Open prostatectomy:
- 35 1) #9 AND prostatectomy AND (open OR invasive)
- 36 Prostatic stents:
- 37 1) #9 AND (stent* OR stents OR endoprothes*)
- 38 Transurethral incision of the prostate (TUIP):
- 39 1) #9 AND (“Transurethral incision” OR “TUIP”)
- 40 Transurethral microwave therapy (TUMT) of the prostate:
- 41 1) #9 AND (microwaves(164) OR microwave* OR “TUMT”)

- 1 Transurethral needle ablation (TUNA) of the prostate:
- 2 1) #9 AND (“Transurethral needle ablation” OR (needle AND ablat*) OR
- 3 radiofrequency OR “radio-frequency” OR “radio frequency” OR “RF” OR
- 4 “TUNA”)
- 5 Transurethral resection of the prostate (TURP):
- 6 1) #9 AND (“Transurethral resection” OR “TURP”)
- 7 Transurethral vaporization of the prostate (TUV):
- 8 1) #9 AND (electrovaporization OR “TUV” OR vaporization OR “vapor-cut”
- 9 OR rotoresection OR “TUVRP” OR rotoresect* OR gyrus OR wing)
- 10 2) #9 AND (electrocoagulation OR electrosurgery OR electrosurgical OR
- 11 electrocautery OR loop)
- 12 3) #9 AND (“Transurethral evaporation” OR “TUEP”)
- 13 4) #1 OR #2 OR #3
- 14 Watchful-waiting:
- 15 1) #9 AND (“watchful-waiting” OR “watchful waiting”)
- 16 2) #9 AND (“untreated”[ab] OR “non-treatment”)
- 17 3) #1 OR #2
- 18 Water-induced thermotherapy (WIT):
- 19 1) #9 AND (water[tw] OR water(164)) AND (Hyperthermia, induced(164) OR
- 20 thermotherapy OR thermal*)
- 21 2) #9 AND thermoablation
- 22 3) #9 AND (“water-induced” OR “WIT”)
- 23 4) #9 AND thermoflex
- 24 5) #9 AND (“hot-water” OR (hot AND water))
- 25 6) #2 OR #3 OR #4 OR #5

1 **EMBASE searches**

2 Below is the search strategy we used for EMBASE:

- 3 S1 s prostat?(2n)(hyperplasia or hypertrophy)
4 S2 s benign()prostatic()hyperplasia or bph
5 S3 s s1 or s2
6 S4 s s3 and py=1989:2003
7 S5 s s4/eng
8 S6 s s5/human
9 S7 s s6 and (urinary()tract()obstruction or prostatectomy of intermethod()comparison
10 or transurethral()resection or laser()surgery or Transurethral()needle()ablation)
11 S8 s s6 and (TURP or TUIP or TUMT or TUNA or TUVP or TUEP or VLAP or
12 HIFU or WIT)
13 S9 s s6 and (prostatectomy and Transurethral and resect?)
14 S10 s s6 and (microwaves/de or microwave)
15 S11 s s6 and (Transurethral()needle()ablation or (needle and ablat?) or radiofrequency
16 or radio()frequency or rf)
17 S12 s s6 and (prostatectomy and (open or invasive or traditional))
18 S13 s s6 and (Transurethral and incision)
19 S14 s s6 and (Transurethral()resection or turp or tur)
20 S15 s s6 and (stent? Or stents/de)
21 S16 s s6 and (balloon dilatation/de or (balloon and dilatation))
22 S17 s s6 and (wit or water()induced or ((water/de or water) and (Hyperthermia,
23 induced/de or thermoablation or thermotherapy or thermal?)))
24 S18 s s6 and (hifu or high()intensity()focus()ultrasound)
25 S19 s s6 and (laser surgery/de or (laser and (ablation or interstitial or holmium or
26 Endoscopic)) or elap or vlap or holep or HoLEP)

- 1 S20 s s6 and (electrocoagulation or vaporization or electrosurgery or evaporation or
2 electrosurgical or electrocautery or loop or vapor()cut or tuvrp or gyrus or wing or
3 electrovaporization)
- 4 S21 s s6 and ((alcohol and ablat?) or chemoablat? Or sclerotherap? Or inject?))
- 5 S22 s s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or
6 s19 or s20 or s21
- 7 S23 s s22 and ((controlled study! Or clinical trial! Or randomization or cross-over
8 procedure or double blind procedure or single blind procedure or placebo)/de or
9 double()dummy or double()blind or single()blind or single()dummy)
- 10 S24 s s22 and (sham or random? Or placebo?)
- 11 S25 s s23 or s24
- 12 S26 s s25 not (letter or comment or editorial or news or case()report or notes or
13 conference()paper)
14

1 Appendix D: Excluded Studies

Table D- 1. Excluded studies and reasons for exclusion

Study	Reason for exclusion
Schelin (2002)(249)	Evaluated the use of intraprostatic and periprostatic injections of mepivacaine epinephrine during TUMT; thus, did not evaluate TUMT itself
Isotalo (2001)(250)	All patients received a spiral stent and after two weeks were randomized to receive either finasteride or placebo. Thus, this was a comparison of finasteride, which is beyond the scope of this review.
Petas (2000)(195)	Both treatment groups received ILC, but one received a biodegradable stent after treatment. This study evaluates the post-treatment usefulness of a biodegradable stent rather than ILC or stenting as a treatment itself.
Wada (2000)(251)	Assigned patients to treatments based on prostate size, thus treatment groups were not comparable.
Djavan (1999b)(252)	Although this study evaluates two treatment groups receiving TUMT, the real comparison is between patients who received adjuvant alpha-blockade versus those who did not during their TUMT treatment.
Lukkarinen (1999)(253)	All patients received balloon dilation and were randomized into those who received finasteride or placebo. Thus, this was a comparison of finasteride, which is beyond the scope of this review.
Shalev (1999)(254)	This was a nonrandomized, retrospective comparison of acute myocardial infarction rates after TURP and open prostatectomy. The patients were assigned treatment on the basis of prostate size, and so were not matched.
Eliasson (1998)(255)	This was a comparison of results for helical coil TUMT versus filament TUMT. The results were stratified according to response, rather than according to treatment.
Devonec & Dahlstrand (1998)(256)	Both treatment groups received TUMT, but one received a temporary stent after TUMT. Evaluated temporary stenting after TUMT rather than TUMT itself.
Grundy (1997)(42)	All patients got TUEVP, but they were randomized to receive either sterile water or glycine as irrigation fluid. Thus, this was a comparison of irrigation fluids rather than different BPH treatments.
Horninger (1997)(257)	Study assigned patients to treatments based on general health or prostate volume. Thus, the comparison groups were not comparable.
Bdesha (1996)(258)	This was a comparison of TURP vs. open prostatectomy. Patients in one group had previously received TUMT, whereas patients in the other group had not. Thus, they were not comparable.

Table D- 1. Excluded studies and reasons for exclusion

Study	Reason for exclusion
De Wildt (1996)(259)	This study combined the results of Francisca et al. (1997)(171) and Ogden et al. (1993)(166) with longer followup time. However, there was an attrition rate of almost 50% after 3 months as patients were unblinded and given new treatment options. Thus, followup included only patients with successful treatment who did not seek additional treatment, which significantly biases results.
Te Slaa (1996)(260)	Study compared patients who received antibiotic prophylaxis for urinary tract infections (prior to BPH treatment) to patients who did not receive antibiotic prophylaxis. Therefore, it did not involve a comparison of treatments for BPH.
Abbou (1994)(258)	Results from patients receiving rectal hyperthermia and patients receiving urethral hyperthermia were combined.
Montorsi (1992)(187)	Transrectal hyperthermia. Treatment groups divided by age and thus not readily comparable.
Andersen (1990)(261)	This was a retrospective, nonrandomized comparison of mortality after TURP and open prostatectomy. The patients in the two groups were not matched and had different characteristics and disease severity.
Roos (1989)(262)	This was a retrospective, nonrandomized comparison of mortality and reoperation after TURP and open prostatectomy. The patients in the two groups were not matched and had different characteristics and disease severity.
Edwards (1982)(263)	This nonrandomized comparison of TUIP to TURP assigned treatment on the basis of prostate size, therefore the groups were not comparable.

1 Appendix E: Treatment Acronyms and

2 Abbreviations in Text and Evidence Tables

Table E- 1. Description of acronyms and short phrases to denote treatments

Short phrase	Description
Balloon	Balloon dilation
CLAP	Contact laser ablation of the prostate
Cystoscopy	Insertion of endoscope, as control for balloon dilation
Expanding stent	Stent that expands once inserted
Fixed stent	Stent that does not expand once inserted
HIFU	High intensity focused ultrasound
HoLAP	Holmium laser ablation of the prostate
HoLRP	Holmium laser resection of the prostate
HoLEP	Holmium laser enucleation of the prostate
Hybrid laser	Hybrid laser technique
ILC	Interstitial laser coagulation
ILC with stent	Interstitial laser coagulation with stent
Medication	Treatment with medication only
No treatment	No treatment intervention or conservative management
Open prostX	Open prostatectomy
Sham	Imitation surgical procedure in which no prostate tissue is removed
Spiral stent	Spiral stent
Stent biodeg.	Temporary biodegradable stent
Temporary catheter	Temporary catheter, as control for temporary biodegradable stent
TRH 3-5x	Transrectal hyperthermia 3-5 applications
TRH 3-5x + meds	Transrectal hyperthermia 3-5 applications, with medication
TRH 6-10x	Transrectal hyperthermia 6-10 applications
TRH 6-10x + meds	Transrectal hyperthermia 6-10 applications, with medication
TRH 6-10x no cath.	Transrectal hyperthermia 6-10 applications, no catheterization
TUCT	Temporary urethral catheter (a form of sham treatment)
TUEVP	Transurethral electrovaporization of the prostate
TUIP	Transurethral incision of the prostate
TULIP	Transurethral ultrasound-guided laser incision of the prostate
TUMT	Transurethral microwave thermotherapy
TUMT 3 sessions	Transurethral microwave thermotherapy, 3 sessions
TUMT 30 min.	Transurethral microwave thermotherapy for 30 minutes
TUMT 6 sessions	Transurethral microwave thermotherapy, 6 sessions
TUMT high dose apex	Transurethral microwave thermotherapy, high dose, focused on the apex of the prostate

Table E- 1. Description of acronyms and short phrases to denote treatments

Short phrase	Description
TUMT high dose base	Transurethral microwave thermotherapy, high dose, focused on the base of the prostate
TUMT low dose apex	Transurethral microwave thermotherapy, low dose, focused on the apex of the prostate
TUNA	Transurethral needle ablation of the prostate
TUR syndrome	Transurethral resection syndrome
TURP	Transurethral resection of the prostate
TUT	Transurethral thermotherapy
VLAP	Visual laser ablation of the prostate
VLAP 1 catheter	Visual laser ablation of the prostate with one indwelling catheter
VLAP 2 catheters	Visual laser ablation of the prostate with indwelling and suprapubic catheters
VLAP DB	Visual laser ablation of the prostate with debridement
VLAP high power	Visual laser ablation of the prostate, high power
VLAP KTP	Visual laser ablation of the prostate using KTP fiber
VLAP low power	Visual laser ablation of the prostate, low power
VLAP painting	Visual laser ablation of the prostate, painting technique
VLAP with stent	Visual laser ablation of the prostate with stent
WIT	Water-induced thermotherapy

1

Table E- 2. Abbreviations in Evidence Tables

Table type	Abbreviations
Study Details	<p>N – No NC – Not calculable NR – Not reported Y – Yes Reported Outcomes: S – Symptoms T –Technical measures A – Adverse effects R – Retreatment Q – Quality of life P or Peri – Perioperative N enrolled – The number of patients enrolled in the two groups for this treatment comparison</p>
Patient Inclusion Criteria	<p>cc – cubic centimeters E – Patients were excluded for this characteristic g – grams I – Patients were included even if they had this characteristic IPSS – International Prostate Symptom Score (AUA) NR – Not reported PSA – Prostate specific antigen PVR (mL) – Postvoid Residual Volume in milliliters Qmax (mL/sec) – Maximum urinary flow rate in milliliters per second umol/L – Micromoles per liter UTI – Urinary tract infection</p>
Treatment Details	<p>Ch – Charr (equivalent to French) F or Fr – French (gauge measurement) KTP – Potassium titanyl phosphate yttrium-aluminum-garnet fiber MHz – Megahertz N – Number Nd:YAG – Neodymium:yttrium-aluminum-garnet fiber NR – Not reported tid – Three times daily W – Watt</p>
Patient characteristics	<p>I BO – Barosky irritative score Md – Median Mn – Mean N – Number of patients NR – Not reported O BO – Barosky obstructive score PSA – Prostate specific antigen PVR – Post-void residual volume SD – Standard deviation SE – Standard error of the mean</p>

Table E- 2. Abbreviations in Evidence Tables

Table type	Abbreviations
Results and Change Comparisons	%chg – Percentage change from baseline %ile – Percentile 95% CI – 95% confidence interval Diff – Difference from baseline ICS – International Continence Society questionnaire IQR – Interquartile range md – Median mn – Mean N – Number of patients NR – Not reported NS – Not significant num pts – Number of patients Peri or P – Perioperative Post-op – Postoperative Q – Flow rate (quotient of volume/time) Ratio – Ratio of postoperative measure to baseline Rg – Range SD – Standard deviation SE – Standard error SEM – Standard error of the mean Sig. – Statistically significant SIR – Siroky maximum flow nomogram, expressed in standard deviation (SD) units.

1

1 **Appendix F: FDA Cleared or Approved**
 2 **Indications for Devices Used in**
 3 **BPH Treatments**

4 The following information was retrieved by ECRI’s database search staff, by querying
 5 FDA’s PMA and 510k databases online at <http://www.fda.gov/cdrh/>. The information
 6 provided reflects all available information specific to BPH that was available through
 7 FDA. Note that many devices, particularly lasers, are FDA cleared for general
 8 indications, rather than for BPH specifically. If the cleared indications for a particular
 9 device did not mention BPH specifically, or was approved as a predicated device by the
 10 510(k) process, we did not include information about that device in this table.

11 **Table F- 1. FDA Regulation Status For BPH Treatment Devices**

Treatment	Device (Manufacturer)	FDA approved/cleared urological indications	FDA approved/cleared contraindications
Laser procedures	CL MD Laser Systems (SLT)	CLAP – prostates up to 45 grams VLAP – prostates up to 75 grams	No details available
	Right Angle and Optilase Lasers (Trimedyne)	For coagulation of soft tissue for prostatectomy in the treatment of BPH (no further details available)	No details available
	Medilas D Laser family (Dornier Medtech)	>Age 50 Median and/or lateral lobes ranging from 28-85 cc	No details available
	Indigo® OPTIMA Laser System (Ethicon Endo-Surgery, Inc.)	Symptoms of BPH (Nothing more specific)	No details available

EPC Report: Treatments for Benign Prostatic Hyperplasia

Treatment	Device (Manufacturer)	FDA approved/cleared urological indications	FDA approved/cleared contraindications
RFNA (TUNA®)	TUNA® (Medtronic)	Age >50 years Prostate size 20-50 cc Symptoms due to urinary flow obstruction secondary to BPH	Active UTI Neurogenic bladder Severe urethral stricture Bleeding disorders or patients taking anticoagulation medication unless antiplatelet meds have been discontinued for at least 10 days ASA Class group V patients Prostatic or bladder cancer Prostate gland <34 mm or >80 mm in transverse diameter Prosthetic device that may interfere with procedure Prostates previously treated with non-pharmacological therapies Presence of cardiac pacemaker, implantable defibrillator, or malleable penile implants Presence of implantable neurostimulation system.
HIFU	Sonablate® 500 System (Focus Surgery Inc.)	Not yet cleared by FDA	Not yet cleared by FDA
TUMT	Prostatron (Urologix)	Prostatron 2.0 (60 W max): Prostatic length of 35-50 mm Prostatron 2.5 (70 W max): Prostatic length of 25-50 mm Benefits of obstructive improvement outweigh the attendant risks	Peripheral artery disease with intermittent claudication Leriche's syndrome Prostate or bladder cancer Severe urethral stricture Cardiac pacemaker, implantable defibrillator, or metallic implant in hip, pelvis, or femur.
	Targis (Urologix)	Prostatic length of 30-50 mm Prostatic urethra length of 25-35 mm	Prior pelvic radiation (Other contraindications do exist but full product labeling information was not available.)

EPC Report: Treatments for Benign Prostatic Hyperplasia

Treatment	Device (Manufacturer)	FDA approved/cleared urological indications	FDA approved/cleared contraindications
TUMT	CoreTherm (Prostalund)	Prostate size of 30-100 g and length ≥ 35 mm	Severe urethral stricture Penile or urinary sphincter implants Previous radiation of pelvic region Bladder cancer Active prostatitis Active UTI Previous prostate or rectal surgery Wish to preserve fertility Implanted defibrillators, pacemakers, or other active implant Metallic implant in prostate treatment area Peripheral artery disease with inter
	TMX 2000 (Thermatrix)	Prostatic urethra length ≥ 30 mm Total prostate volume 30-100 cc Patients with bladder or prostate cancer CAN receive this treatment.	No details available.

EPC Report: Treatments for Benign Prostatic Hyperplasia

Treatment	Device (Manufacturer)	FDA approved/cleared urological indications	FDA approved/cleared contraindications
	Prolieve™ System (Celsion)	Prostate size 20-80 grams Prostatic urethra length 1.2 cm – 5.5 cm Patients in whom drug therapy is typically indicated.	Patients whose pain has been relieved by any other treatment Severe urethral stricture Current urinary or prostatic infection Penile or urinary sphincter implant Peripheral artery disease with intermittent claudication Protruding middle lobe resulting in obstruction Evidence of prostate or bladder cancer Presence of metallic implants in pelvic region Presence of implanted cardiac pacemakers or defibrillators Previous transurethral prostatectomy Interest in preservation of fertility History of pelvic radiation Coagulation disorder Renal impairment Neurologic disorders affecting bladder function Bladder stones
Prostatic Stents	Urolume™ Endourethral Wallstent ^R Prosthesis (American Medical Systems, Inc.)	To relieve prostatic obstruction secondary to benign prostatic hypertrophy (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	Fracture distraction defects of the posterior urethra; the device is not intended for temporary use
Water Induced Thermotherapy	Thermoflex™ WIT System (Argomed, Inc.)	>50 years old Symptoms of urinary obstruction Prostatic length 2.0-6.4 cm	No details available

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