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EXECUTIVE EDUCATION

Biodesign in BPH

Needs Finding in a Competitive—and Evolving—Field

CASE STUDY 2015

STANFORD biodesign

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Needs Finding in a Competitive—and Evolving—Field

"Our challenge should be neither to reinvent the wheel, nor to design a better one, but to create something better altogether."

–Mark A. Cabelin, Alexis E. Te, Steven A. Kaplan, "Benign Prostatic Hyperplasia: Challenges for the New Millennium," Current Opinion in Urology, 2000, 10:301-306

Benign prostatic hyperplasia (BPH) can have a profound impact on men's quality of life as they age. And, unfortunately, the side effects of many available treatments can be as bad as—if not worse than—living with the condition itself. For decades, scores of innovators and companies have sought to disrupt the standard of care for BPH, but only a few have succeeded in sustainably altering prevailing treatment paradigms. This case study examines the innovation landscape in BPH and how two companies have been able to define, develop, and commercialize products that have made (or seemed poised to make) lasting improvements in the field.

WRITTEN AND PREPARED BY THE BIODESIGN TEAM

INTRODUCTION

In the US alone, roughly half of men over the age of 50 suffer from benign prostatic hyperplasia (BPH), and by the age of 80, up to 90 percent are affected.[1] Since the 1920s, the gold standard treatment for severely symptomatic BPH has been transurethral resection of the prostate (TURP), an effective but highly invasive surgical procedure with many unpleasant side effects.[2] The well-known drawbacks of TURP, along with the substantial size of the BPH market and negative effect of the condition on men's quality of life, have generated decades of innovator and investor interest in developing better treatments. However, most efforts to invent new medical technologies and procedures to address BPH either failed outright or were only marginally effective, resulting in considerable corporate and venture frustration and a legacy of patient and provider dissatisfaction. It wasn't until the mid-2000s that a few select companies began making inroads in sustainably expanding the treatment landscape for BPH.

Why did so many innovators fail in BPH, and what sets apart those few that were able to finally disrupt established treatment paradigms? One explanation is that that, over time, the successful medtech companies were able to learn from the experiences of their predecessors. However, when viewed through the lens of biodesign, another more substantive difference may be that the successful innovators utilized a more needs-driven approach to bringing solutions forward in the space. This case study explores the importance of getting the need right—that is, accurately framing a need at the outset, staying true to the need throughout the development process, and recognizing how needs within a solution space evolve as new technologies are introduced and adopted. To illustrate these concepts, the case looks closely at two companies focusing on BPH: Laserscope, whose GreenLight laser was the earliest device technology to successfully challenge the established standard of care, and NeoTract, which entered the space subsequently with a non-surgical implant called UroLift.

This case study explores the importance of getting the need right...and recognizing how needs in a solution space evolve as new technologies are introduced and adopted.

THE COMPETITIVE LANDSCAPE IN BPH IN THE LATE 1990s AND EARLY 2000s

In the late 1990s and early 2000s, medtech companies launched a flurry of innovation activity in BPH seeking to improve the treatment landscape, which was dominated by drug therapy and TURP. (Swipe to the next section to read the feature on BPH and its treatment.)

Some of these efforts reflected the "technology du jour," meaning that interventions such as balloon dilation and stents that had proved successful in other specialties were applied to BPH. "The thinking was, 'Well, if this works in the coronary arteries, it is certainly going to work in the prostate,'" recalled Thom Gunderson, a managing director and senior med-tech analyst for Piper Jaffray, who has followed the urology space for more than 20 years.[3] "It didn't seem like there was much thought given to the anatomy or physiology of the two different structures." Not surprisingly, both of these particular approaches failed relatively quickly.[4]

Other new minimally-invasive approaches sought to reduce procedural trauma by causing cell necrosis (death), rather than surgically resecting

the tissue (as was the case with TURP). These new procedures were based on delivering energy to the prostate in various forms, such as transurethral microwave heat treatment (TUMT), in which a probe inserted into the urethra delivered microwave energy to destroy the surrounding prostate, and transurethral needle ablation of the prostate (TUNA), in which needles placed into the lobes of the prostate used radiofrequency energy to create thermal lesions. Another approach, visual laser ablation of the prostate or VLAP, used laser energy to cause coagulative necrosis of the inner prostatic tissue. Following the procedure, the treated tissue would slough away over four to eight weeks, ultimately relieving the obstruction of the urethra.

Although some of these new approaches achieved varying levels of adoption, none met the bar set by TURP for symptom improvement. Most also had unpleasant side effects, including persistent irritative voiding symptoms and temporary urinary retention.[5] VLAP, in particular, was effective at improving urinary outcomes but had significant drawbacks such as a lengthy, painful recovery that required extended catheterization as the treated tissue slowly sloughed away.[6]

Yet another problem with many of the newer BPH procedures and devices involved the lack of sufficient long-term data to accurately predict their performance and success. US Food and Drug Administration (FDA) regulatory requirements at the time enabled many BPH therapies to enter the market with as little as three months of bench and safety data. Recalled Gunderson, "I remember going to an American Urological Association [AUA] meeting and hearing a presentation of long term results on a new therapy for BPH. It all looked really good until one of the doctors in the crowd asked how many patients were in the long-term study and the answer was seven. So everyone was interested in selling as much as they could, as fast as they could, but no one was looking towards the future and realizing that they needed clinical data."

As a result, many clinicians and patients were disappointed by the outcomes of the new treatments, and numerous techniques and devices were abandoned. As medical device veteran Eric Reuter, summarized, "The landscape at the time was littered with technologies that either failed, or weren't competitive with TURP in terms of clinical efficacy. There was a lot of activity in the space, but nothing that had knocked TURP off its pedestal as the standard of care."

LASERSCOPE AND THE BLOODLESS TURP

Reuter, the former vice president of R&D at Laserscope, took over as CEO of the company in 1999 to help orchestrate a turnaround. As part of his efforts to revitalize Laserscope, which sold a variety of medical laser systems in different therapeutic areas, he met with one of the company's urologist customers, Dr. Reza Malek of the Mayo Clinic. For many months, Malek had been testing a prototype of one of Laserscope's surgical laser products to treat BPH. The prototype laser was a potassium-titanyl phosphate (KTP) laser, which produced a green visible laser light beat beam with a short (532 nanometer) wavelength. The KTP laser wavelength has unique properties; its energy is preferentially and highly absorbed by the hemoglobin in blood, but only minimally absorbed by water. "The concept was to use a fiber optic delivery device to direct a focused beam of laser light energy through a standard cystoscope to the operative site, where it would vaporize the prostate tissue while also providing immediate coagulation," said Reuter. Elaborating on how this would work, he continued, "The laser energy travels through the surgical saline with no appreciable absorption, gets largely concentrated into the superficial prostate tissue, and vaporizes it. A percentage of that energy is also deeply-enough absorbed to coagulate the adjacent tissue to the depth of about a millimeter. The combination largely eliminates intra-operative and post-operative bleeding and minimizes dysuria (painful urination) associated with too much heating and injury."

"Looking back, it was one of those rare 'epiphany moments.' We realized that we had recognized a significant clinical need...and that we had the unique technological competencies and skills necessary to meet that need."

The early results were encouraging, and it was apparent to Reuter that a much higher-power system could have the potential to change the way BPH was treated. "I took one look at what Dr. Malek had demonstrated and I immediately made the decision that we were going to go after TURP. And I felt in that moment that we were going to win," said Reuter. "Looking back, it was one of those rare 'epiphany moments.' We realized that we had recognized a significant clinical need for a procedure that would reduce the side effect profile of TURP while achieving comparable clinical outcomes, and that we had the unique technological competencies and skills necessary to meet that need. Although I knew there would be significant challenges ahead, it was a very exciting time and this feeling grew stronger as we gained more clinical experience," he recalled.

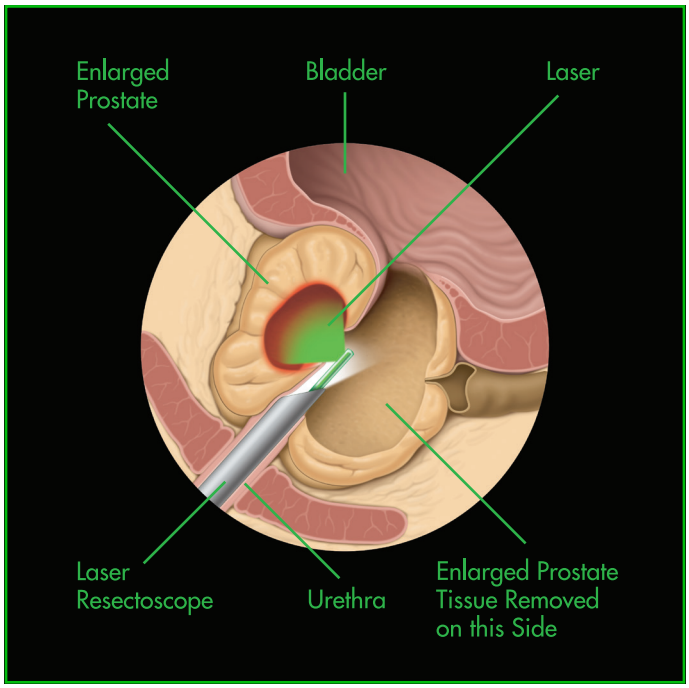


FIGURE 1

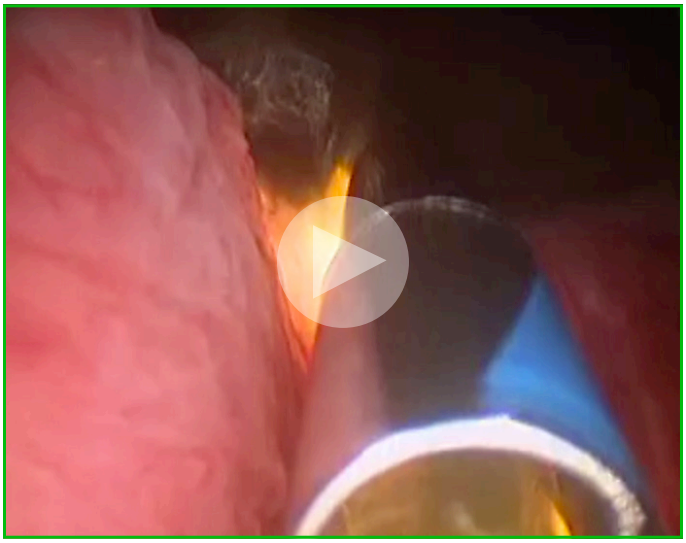
With PVP, the heat from the laser vaporizes parts of the prostate tissue.

Source: European Association of Urology, "EAU Patient Information on Benign Prostatic Enlargement," http://patients.uroweb.org (accessed November 2014).

Laserscope's primary goal was to achieve better clinical outcomes and an improved patient experience. As Reuter summarized, "TURP was a messy, bloody procedure with numerous intraoperative and postoperative complications that included bleeding, TUR syndrome [in which excess absorption of the electrolyte-free irrigating fluid used during the procedure causes a dangerous sodium imbalance in the patient], urinary incontinence, urethral strictures [a narrowing of the urethra caused by inflammation or scar tissue], and all kinds of sexual dysfunction. There were a lot of patients who were having really significant problems and we made it our fundamental mission to give them a better solution."

A secondary but equally important goal was to improve the procedure experience for the physicians. TURP was considered a technically challenging procedure to perform.[7] Explained Reuter, "Essentially, TURP works by carving out pieces of tissue with an electrocautery loop, so there was a lot of bleeding during the operation. The bleeding was not only bad for the patient, but it clouded the urologist's field of view and made it difficult to see where the loop was ablating. By observing in the OR, we realized that they just couldn't see anything some of the time. And so one of the reasons why the typical learning curve for TURP is 30 to 50 procedures is that the new residents had to learn how to 'feel their way around' without good visualization. We wanted to eliminate or at least dramatically reduce that." Reuter continued, "It was also clear that a lot of physicians were having trouble. Few individual surgeons would freely admit to having a problem, but the aggregate data was compelling." As Gunderson summarized, "Not only were patients looking for something better, because TURP sounded like a god-awful procedure, but the doctors knew that they were not always getting perfect results. They remember the ones that didn't work out that well because they nicked something or had excessive bleeding or whatever. And now they have an unhappy patient that, months later, continues to call."

In 2001, Laserscope commercially launched the GreenLight laser and fiber optic disposable delivery device for the treatment of symptomatic BPH (see Figure 1). In the procedure, known as photoselective



VIDEO 1

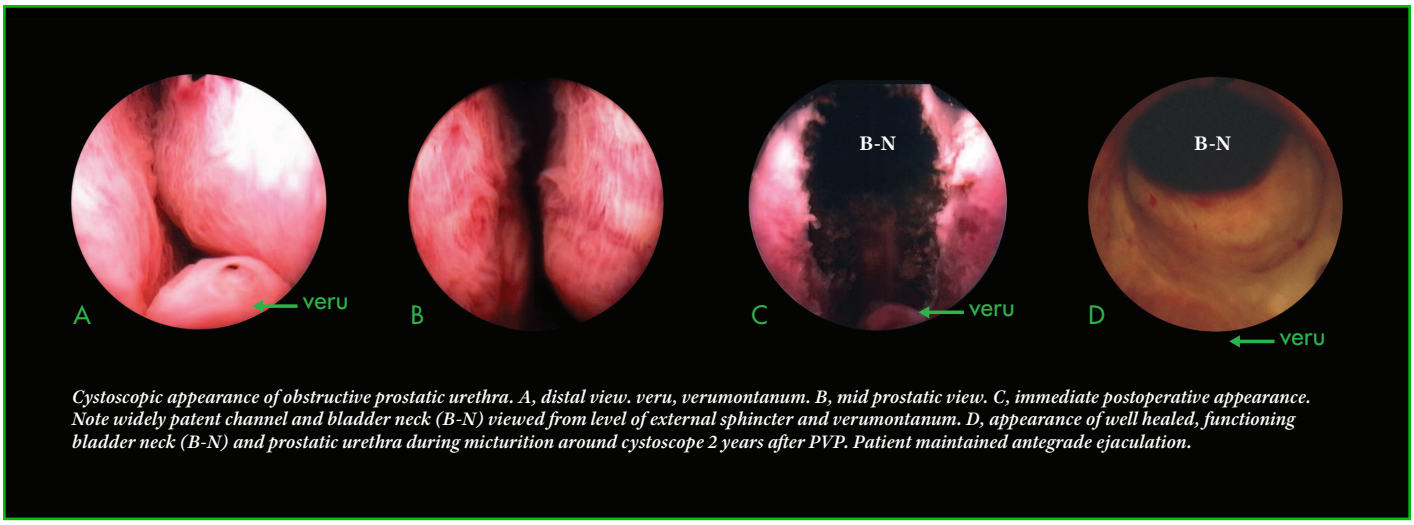
Photoselective Vaporization of the Prostate. This patient has a large median prostatic lobe that is vaporized first to open the bladder neck, followed by treatment of the lateral prostatic lobes.

Click on image above or go to: https://www.youtube.com/watch?v=DEdVuwPGC24

Source: With permission from AMS.

vaporization of the prostate (PVP), the physician uses the laser to remove excess prostate tissue and create a larger channel around the urethra, generating a rapid flow improvement, and relief of lower urinary tract symptoms (LUTS). (See Video 1.) Importantly, unlike most of the new solutions that preceded it, GreenLight entered the market with a solid two years of data behind it, starting with Malek's first ten patient study in 1998, followed by 55 patient study published in 2000. The data validated the safety and efficacy of the procedure, which helped overcome the reluctance of urologists to try yet another new approach to BPH treatment. "There was a tremendous amount of skepticism from payers, physicians, and hospital administrators because there were a lot of 'bones' of older laser systems littering the basements of a lot of hospitals," Reuter noted. "This made getting our product adopted much more difficult because many physicians automatically assumed that 'all lasers were created equal.'"

By 2004, Laserscope was able to publish 12-month outcomes from its first multi-center prospective US trial[8] of 139 patients that verified the procedure provided immediate symptomatic and functional relief of bladder outlet obstruction as measured by metrics such as the maximum rate of urinary flow (QMax), post-void residual urine (PVR), and score on the American Urological Association Symptom Index, (AUA-SI, also called the International Prostate Symptom Score or IPSS), as well as durable results at 1 year. The study found that the high vaporization energy of the KTP laser allowed the creation of an open cavity in the prostate similar to TURP, but with excellent control of bleeding (eliminating clinically significant blood loss and the need for blood transfusions). There was also no risk of TUR syndrome because normal saline could be used as irrigation fluid during the procedure. Offering, "more precise tissue removal with less trauma,"[9] PVP could be performed with general or regional anesthesia, produced short catheter times (generally less than 24 hours), and made it possible for most patients to resume normal non-strenuous activities within 2–3 days. Adverse events were mostly transient, including dysuria (9.4 percent), mild to moderate amounts of blood in the urine (8.6 percent), short-term urinary incontinence (6.5 percent), and urinary retention



Cystoscopic appearance of obstructive prostatic urethra. A, distal view. veru, verumontanum. B, mid prostatic view. C, immediate postoperative appearance. Note widely patent channel and bladder neck (B-N) viewed from level of external sphincter and verumontanum. D, appearance of well healed, functioning bladder neck (B-N) and prostatic urethra during micturition around cystoscope 2 years after PVP. Patient maintained antegrade ejaculation.

FIGURE 2

Obstructive prostatic urethra before PVP (A and B), immediately post-PVP procedure (C), and two years after PVP (D).

Source: Reprinted from *The Journal of Urology*, Volume 174, Reza S. Malek, Randall S. Kuntzman, David M. Barrett, "Photoselective Potassium-Titanyl-Phosphate Laser Vaporization of the Benign Obstructive Prostate: Observations On Long-Term Outcomes," October 2005, pp. 1344–1348, with permission from Elsevier.

requiring re-catheterization (5 percent). While the study found no new incidences of erectile dysfunction following the procedure, 36 percent of the sexually active patients in the study experienced retrograde ejaculation (see BPH Feature), an outcome that was not unexpected for a procedure that "effectively vaporizes the bladder neck."[10]

The published data, along with the support of key opinion leaders who began using the procedure with good results in the US and internationally, helped Laserscope drive adoption. "We were very careful where we launched the product," recalled Reuter. "We started with individual centers of excellence and moved out from there to ensure that physicians had proper training. In the first two to three years, we had a lot of significant successes with the procedure." However, he pointed to two factors that "put GreenLight on the map." The first dealt with facility reimbursement. Laserscope was able to get a new technology code from CMS based on its dramatically lower side effect profile as compared to TURP. "Although the early materials costs for PVP were considerably higher than for a TURP procedure, our clinical results demonstrated that there was a tremendous cost savings to the healthcare system because of the improved side effect profile. PVP was essentially bloodless, it was typically an outpatient procedure, and most patients went home without a catheter within 24 hours and could return to work in two or three days," Reuter reiterated. The second factor that helped drive PVP uptake was direct demand from patients as they learned about the procedure from physicians and other patients. "We heard of patients or their spouses and friends starting blogs, and posting their results on forums. In general, there was a sense of great excitement from many patients who had struggled with and often suffered with their symptoms for years." (See Figure 2.)

As PVP gradually gained market share against TURP, the pace of innovation in the sector quieted. "Lasers were the winner," summed up Josh Makower, founder of medical device incubator ExploraMed. "Everyone else had failed. Millions in venture money had been spent and lost. And the space was once again dead to innovation."

Yet, over the next few years, the comparative differences between TURP and PVP narrowed. For one thing, technological improvements and new teaching methods improved TURP outcomes and reduced complications.[11] Additionally, as PVP was adopted by a broader physician-base in environments that differed from the clinical trial setting, real-world outcomes were not as consistently efficacious. Ultimately, both therapies were reported to achieve similar intermediate-term outcomes with regard to urinary function, with key differences between the two approaches including length of hospital stay and catheterization time (both shorter with PVP), operative time (longer with PVP), re-intervention rate (higher with PVP), and postoperative complications of blood transfusion and clot retention (significantly less with PVP).[12,13] With regard to sexual function, both therapies could cause loss of ejaculatory function; and their effect on erectile function remained unclear (and somewhat controversial).[14]

"If you could get treated in a doctor's office, or in a very light sedation outpatient surgical center, and get durable symptom relief with even fewer side effects than PVP via a simple-to-perform procedure, that would be the Holy Grail for BPH treatment."

In 2006, AMS acquired Laserscope in a deal valued at $715 million.[15] Despite PVP's acceptance as an alternative to TURP, AMS still had some challenges to overcome with the GreenLight technology. "Many TURP physicians were just more comfortable with the loop," explained Reuter. "And they did not feel that GreenLight was fast enough. Given the longer procedure time, GreenLight still had a problem with post-operative dysuria—you're in there longer with the heat and that causes irritation and post-operative pain for the patient." Perhaps most important was the fact that, as Reuter pointed out, PVP was still a surgical procedure that, although considerably easier to learn that TURP, still relied on physician skill to be successful. Looking forward, in terms of future innovation in the BPH field, Reuter felt that, "If you could get treated in a doctor's office, or in a very light sedation outpatient surgical center, and get durable symptom relief with even fewer side effects than PVP via a simple-to-perform procedure, that would be the Holy Grail for BPH treatment."

NEOTRACT AND ITS NON-SURGICAL APPROACH

Defining and Researching the Need

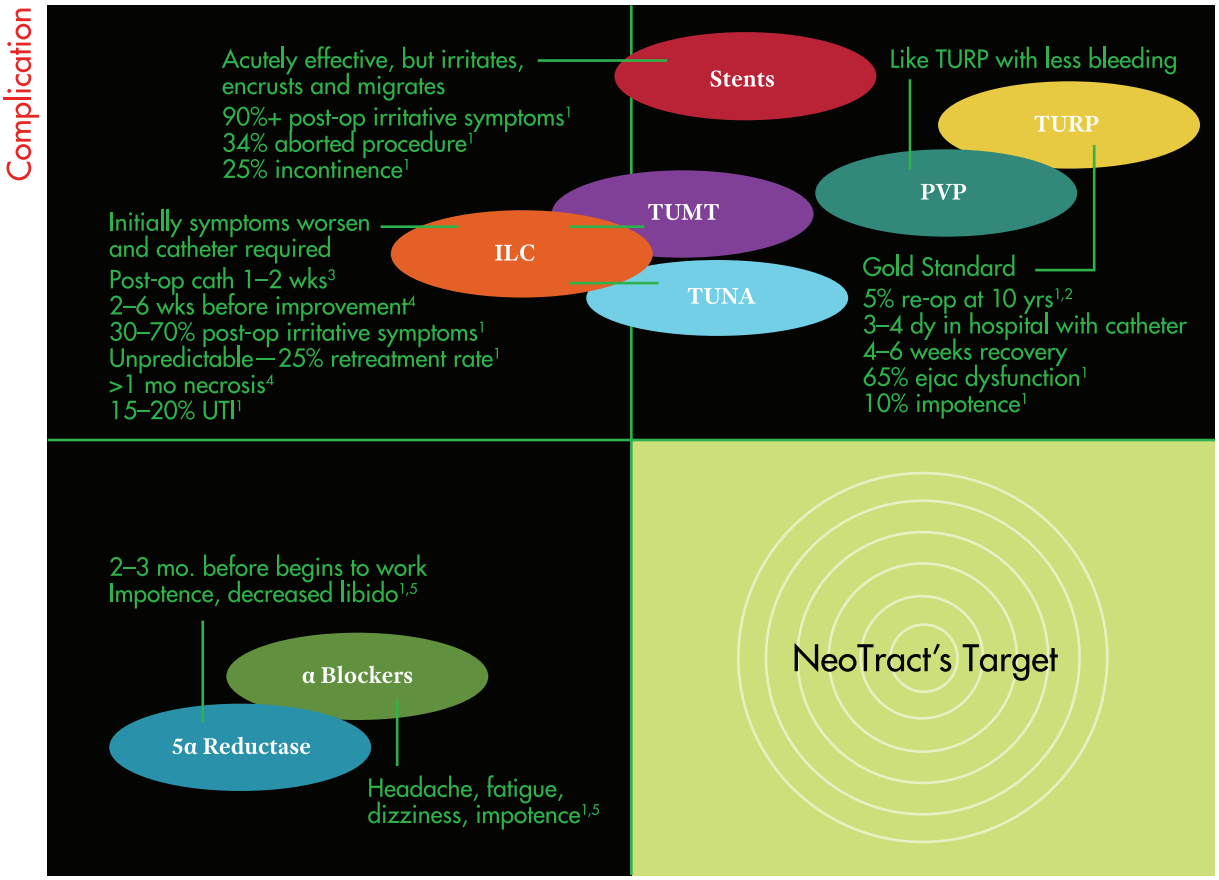
In 2004, as Laserscope released its 12-month clinical data on PVP, experienced medical device innovators Ted Lamson and Josh Makower took an interest in BPH. They were going through the needs finding process to identify opportunities to form a new company and had yet to decide upon a strategic focus area. The two men were investigating potential projects in orthopedics, cardiology, and urology. Lamson's interest in BPH was piqued by the fact that two of his family members were dealing with urologic issues that were tangentially related to the condition. "For both of them, there really seemed to be a lack of appropriate treatment options, and it got me personally motivated to look more deeply into the space," he described.

Lamson reached out to Stanford urologist Dr. Harcharan Gill to discuss BPH and to observe some of the current surgical solutions available to patients. "At the time, I had credentials at Stanford, so I was able to go into the operating room. Dr. Gill treated me just like one of his residents, explaining during the TURP procedure what he was doing and why." The clinical immersion and early conversations with Dr. Gill reinforced Lamson's belief that there were opportunities in the space. "This really motivated us to say, 'All right, let's take a look at this. Let's dig in and try to define this need better.'"

To do that, the two men spent roughly three months researching the medical literature to master the disease state fundamentals. "Our goal was to try to become as knowledgeable and proficient in this very specific field (BPH) as anybody out there," said Lamson. At the same time, in order to develop a more hands-on, mechanical understanding, Lamson purchased the equipment of a retiring urologist and hired an active practitioner to spend three days in the cadaver lab with him, teaching him how to use the various tools. "Over the course of a few weeks, I learned how to conduct cystoscopic procedures with a fairly high level of proficiency," he said. "What this meant was that later, when I was observing more procedures in the OR, I could see where the surgeons were being challenged, when they would hit bleeding and why, and how they would deal with that."

At the same time they conducted this deep dive into disease research, Lamson and Makower constructed a detailed a map of the solutions

BPH TREATMENT LANDSCAPE



[1] AUA Guidelines, 2003.
[2] Varkarakis et al., "The Prostate" 58: 248–251, (2004).
[3] Rubenstin J, "Transurethral Microwave Thermotherapy of the Prostate (TUMT)," eMedicine article, July 2004.
[4] Muruve, N, "Transuretheral Needle Ablation of the Prostate (TUNA)," eMedicine article, June 2005.
[5] AUA: Urologyhealth.org.

FIGURE 3

The treatment landscape for BPH in the mid-2000s.

Source: Courtesy of NeoTract.

available to patients with symptomatic BPH (see Figure 3 for a simplified representation). "It had become very obvious to us that there was still a major gap in the treatment spectrum for BPH. On one end were palliative medications that mostly treat the symptoms of the disease and create side effects that are more annoying than the problem for roughly one out of every three men. And on the other end of the spectrum was an invasive surgery that has been around since the 1920s. It does a really good job of solving the problem, but for many patients, it creates other problems that significantly affect the patient's quality of life, like losing a part of their sexual function," Lamson remembered.

The innovators readily agreed that, with the advent of PVP, Laserscope had successfully addressed the most compelling needs related to TURP at the time. "There is no question that Laserscope vastly improved on the TURP procedure by minimizing bleeding and allowing the patients

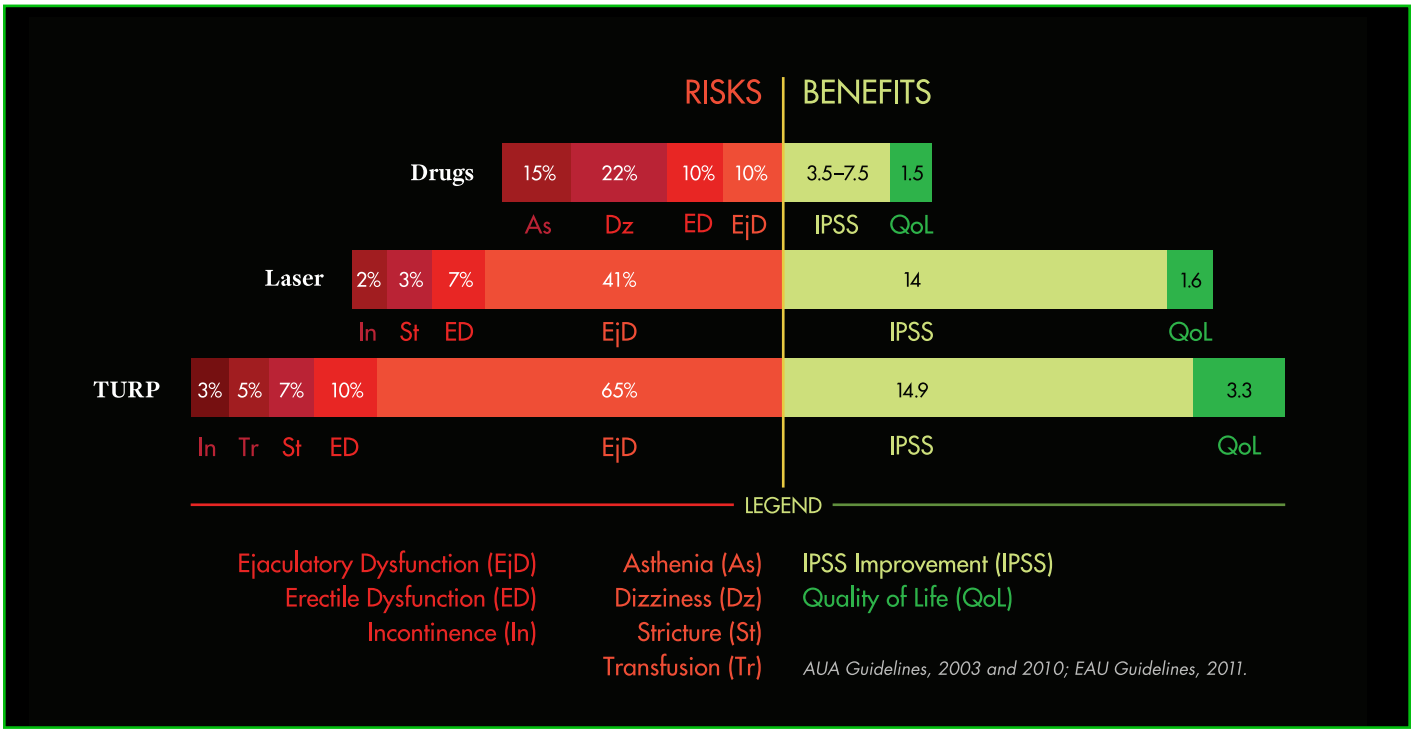


FIGURE 4

Risks and Benefits Associated with Existing Treatments for BPH

Source: Courtesy of NeoTract.

to go home more quickly, which also made the solution more cost effective," said Makower. But Lamson and Makower also felt the need had subsequently evolved. "For patients with anything short of very severe symptoms, BPH is really a quality of life problem—it's not a life or death condition unless it goes untreated for a very long time. So if I put myself in that category as the hypothetical patient, there is a still a huge chasm between taking medication and having someone cut out the inside of my prostate," said Lamson. "Laserscope had been very successful in transitioning a good portion of TURP patients to PVP but what needed to be addressed now was all those men upstream of that the decision to have surgery."

To understand the perspectives of the multiple stakeholders in BPH, Lamson and Makower talked with past patients, potential patients, and men who were in the process of making treatment decisions. They also interviewed urologists in both academic medical centers and private practice. By asking similar questions of patients and physicians, they recognized an important disparity in the way stakeholders in these two groups considered BPH treatment options. "The provider chooses a therapy by matching the efficacy of the procedure to the patient's needs. The patient focuses on the risks associated with each procedure and weighs out his decision that way," said Lamson. "This confirmed the need for a solution that offered the efficacy that the providers required, but that was far less traumatic and had fewer risks and safety concerns than surgery." (See Figure 4.)

Lamson and Makower's research confirmed that the size of the BPH market was attractive if they could devise a solution to address the needs of the roughly 1.3 million of men who discontinued drug therapy because of side effects or lack of efficacy, yet did not elect to have surgery (their preliminary target market). However, they were all too aware that BPH remained a complicated space. According to Lamson, "Our board of directors really challenged our interest in this area because they had seen so many companies come and go." In contrast, Lamson and Makower saw these previous technology failures in BPH as an opportunity. "There was just a ton of experience to learn from. We felt it was a major advantage to come in 5–10 years after there had been all of these efforts to solve this problem and be able to look at all the data, read the publications, and talk to the CEOs and other stakeholders," Lamson commented.

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As the investigative process continued, Lamson and Makower became more deeply engaged in pursuing the need they had characterized as "a highly efficacious, minimally invasive treatment option for men with symptomatic BPH that is fast, easy, and safe to perform to address the treatment gap between medical therapy and TURP/PVP." They set aside the other needs they had been researching in cardiology and orthopedics to devote themselves to this project. Based on their accumulated learnings, Makower and Lamson defined the following "must-have" need criteria as part of their need specification:

- 30-minute procedure
- Local anesthesia
- Immediate, predictable relief of obstructive symptoms
- Patient goes home on the same day, without a catheter
- Quick improvement in irritative symptoms
- Solid two-year sustained results
- No incontinence, erectile dysfunction, migration, or encrustation.

Exploring New Treatment Alternatives

Having fully characterized the need, Lamson and Makower were ready to move into ideation and began brainstorming solutions. "Once you were past lifestyle changes and medications, there were basically two approaches to the treatment of BPH," said Lamson. "One was to cut

out the inner prostatic tissue, and the other was to injure it and cause it to either contract and scar, or die and slough away. Both of those approaches rely on an injure-recover biological process that doesn't link well with how the tissues in that area need to operate for normal urinary and sexual function," he observed. "They also involved a lengthy, uncomfortable recovery period until the patient healed. We were committed to coming up with something different."

"Based on our need specification, we wanted to focus on procedures that could be done in an office environment with a relatively minimally invasive approach," said Makower. "This left us with some sort of tool or catheter-based approach that could be done transurethrally." Several initial ideas to prop open or stent the prostatic urethra were screened against the need criteria and dismissed fairly quickly. "The prostatic urethra is like a triangle," explained Makower. "So if you try to put a circular device or tube in there, there will be little gaps between the device and the tissue. And whenever you have those areas of non-coverage, you are going to have encrustation—it's an absolute recipe for it." Ideas for a shaped insert were also quickly rejected due to the complex morphology of the prostatic urethra. "It has a swooping shape, and variable lumen size that gets bigger and smaller," Makower noted, "so a coil-based system wouldn't work, and neither would a corkscrew shape. It was clear that anything that had a fixed dimension longitudinally and radially was not going to work."

As the innovators continued to brainstorm, a concept that they dubbed "capsular release" emerged. Describing the concept, Makower said, "Think of the prostate gland as a chestnut—a massive piece of material growing and squeezing against a hard outer shell or capsule. There's a lumen inside the middle of this chestnut and, as the gland grows in mass and rigidity, it compresses that lumen because the capsule is fairly rigid—it's sort of a tight connective tissue barrier. So we thought, well, what if we just make a tiny cut in the capsule and release that pressure?" To eliminate the risk of damage that could cause sexual or urinary complications, the cut could be made in the top of the capsule, away from the vascular supply and the nerves. The procedure could be done minimally invasively using a transurethral catheter. "Our vision was to enter the periprostatic space and, with a tiny instrument, slice the capsule just enough so that it opened up and the pressure was released," Makower explained. After some additional concept screening, Makower and Lamson brought in a third engineer-entrepreneur, Joseph Catanese, and decided to take capsular release forward as their lead idea.

Learning from Failure—and Pivoting to Success

The team's first crucial milestone was to design a test to evaluate the fundamental feasibility of the capsular release idea. The key question was whether slicing open part of the prostate capsule would relieve the pressure that was compressing the prostatic urethra and causing urinary symptoms. Given the specificity of the condition, they would need to work on cadavers with BPH. To measure the pressure inside the prostate, they decided to place a balloon inside the organ. "We could blow it up, and it would be constrained by the mass of the prostate. Then we could try to do capsular release and see if the pressure inside the balloon dropped," Makower said. They built a pressure management system inside a balloon, put the balloon into the prostatic urethra, blew it up, and took pressure measurements. "The next step was to try the capsular release, which at this point was done with just a scalpel because we didn't have to develop a minimally invasive device yet," he said. "We started doing the release. We cut out the first layer of the prostate and checked the pressure inside the balloon. No change. We cut the next layer of prostate. No change. We cut the entire capsule, and there was still no change. We started cutting into the mass of the prostate and it was the same, no change–all the way until we opened up the urethra itself. And so the idea failed," Makower described.

For the next month, Lamson, Catanese, and Makower continued to iterate on the experiment to make sure that the failure wasn't due to flaws in the test design. For instance, they revised the balloon, tried making the incisions more slowly, and experimented with different incision sizes. After multiple iterations, the team was ultimately forced to abandon the idea of capsular release.

Undeterred, they began examining their data more closely, trying to advance their understanding. "We didn't want to 'just move on.' We wanted to know why the concept had failed," said Makower. "Something about our theory was wrong and we were determined to figure out what it was and learn from it." The trio continued studying the data from the pressure tests. "For one thing, we wanted to figure out why the balloon, which was supposedly constrained by this massive prostate, was so big before we did anything to relieve the pressure around it," said Makower. "Eventually, we realized was that BPH prostates are tremendously compressible, much more so than a non-BPH prostate. And that led us to the discovery that most of the BPH mass was actually squishy glandular and vascular tissue, not a dense proliferation of cells and connective tissue. So you could physically squeeze the tissue and

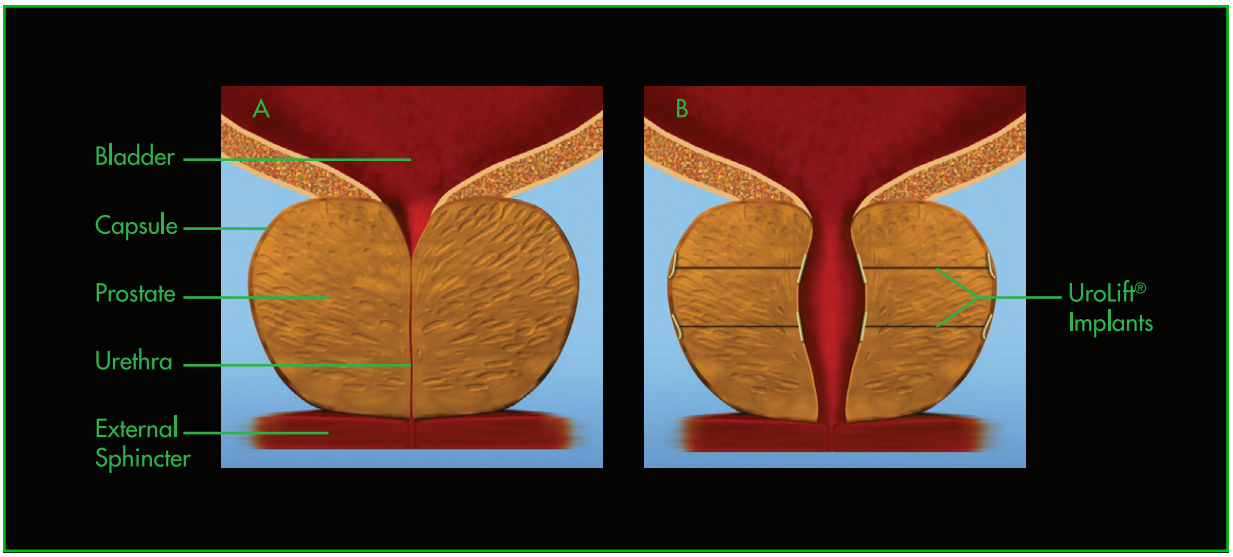


FIGURE 5

A simplified representation of the concept that would become the NeoTract UroLift solution. This diagram shows the prostate obstructed by BPH (A) and after procedure with permanent implants retracting prostatic tissue and increasing prostatic urethral lumen (B).

Source: "The Prostatic Urethral Lift for the Treatment of Lower Urinary Tract Symptoms Associated with Prostate Enlargement Due to Benign Prostatic Hyperplasia: The L.I.F.T. Study," *The Journal of Urology,* December 2013, pp. 2161–2167. Copyright © 2013 American Urological Association Education and Research, Inc.

compress it down, and that would allow the balloon to get very big." The innovators contemplated this insight and realized that their observation was validated by the fact that the BPH drug that worked quickly to relieve symptoms was an alpha blocker, which reduces vascular tone. "So the more vascular pressure there is on the prostate, the more symptomatic the BPH. But if you start constricting blood vessels and relaxing the smooth muscle, the patient gets some relief."

This insight about the compressible nature of the prostatic tissue in BPH led the three men to another approach. "We were able to squeeze three centimeters of thickness down to a centimeter. And so we thought, what if we just went in where the two lateral lobes of the prostate sit next to the urethra, pushed each of them back, away from the urethra, squeezed all the blood and glandular material out, and then just tacked them in place against the capsule wall, like a curtain, on both sides of the urethra?" Makower recalled.

"I remember our first attempt at it and our reaction," said Lamson. "In a cadaver experiment, after looking again at the capsular release work, I instead pushed a K-wire through the prostate from a cystoscope. We taped a size 0 suture to the end of the wire and pulled it through the prostate. I then cut the tip off of a 10-milliliter syringe plunger and threaded it up the suture, followed by—no joke—part of a pen spring. With the suture tensioned, the plunger head compressed the prostate lobe; the spring held it in place; and the prostatic urethra was wide open. We looked at each other and said, 'Whoa! This is what we're going to do. No more balloons and pressure/volume curves!'" (See Figure 5.)

In parallel, the team assessed critical concept screening factors, including IP, regulatory, and reimbursement considerations. Their IP attorney confirmed that they had both patentability and freedom to operate. On the regulatory front, the team felt confident based on expert input that their curtain tie concept would be able to follow the 510(k) pathway, using endoanchor systems and surgical staples as predicates for a general surgery indication. They would then pursue a BPH indication, with interstitial laser coagulation and TUNA devices as predicates (along with the company's own clearance for general surgery). In terms of reimbursement, they were advised that new coding, coverage, and payment mechanisms would be required. To support the creation of a new CPT code, the team planned to conduct a large-scale pivotal trial despite the limited data requirements associated with a typical 510(k). They would also work with key opinion leaders affiliated with the American Urological Association, American College of Surgeons, the Centers for Medicare and Medicaid Services (CMS), and private payers to establish appropriate payment levels for their new technology and procedure.

Based on the reasonably positive evaluation of these factors, said Lamson, "The next question was to determine if this idea would work in live humans. We recognized that there might be a fatal flaw that we couldn't have predicted, like maybe it would be really annoying to have the device in place. So although we were fairly certain we could push back the lobes and open up the urethra, we couldn't be sure whether that would improve symptoms or make things worse because of irritation. Before going any further, we had to get early clinical data to determine whether or not this was really a good idea."

Accordingly, rather than focusing on the development of a streamlined delivery device that could be used under local anesthesia, the innovators pressed forward with an invasive, early version in order to get the procedure into the surgical environment for testing. After meeting all ethical and safety requirements, in December of 2005 they were able to test the procedure on 10 patients in Australia who were on a waitlist for the standard TURP surgery, with the understanding that if the patients awoke from surgery and were not happy with the outcome, they could have the procedure reversed and go on to a regular TURP procedure as planned.

The early results proved the technical feasibility of the concept. "We were able to do the same thing mechanically in humans that we did in

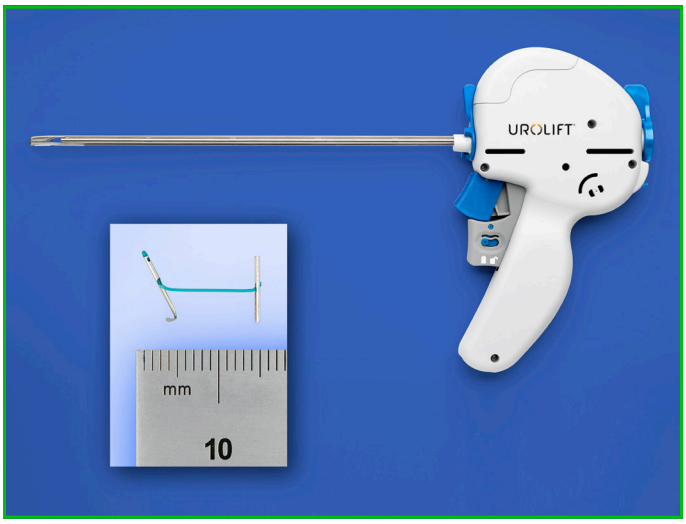
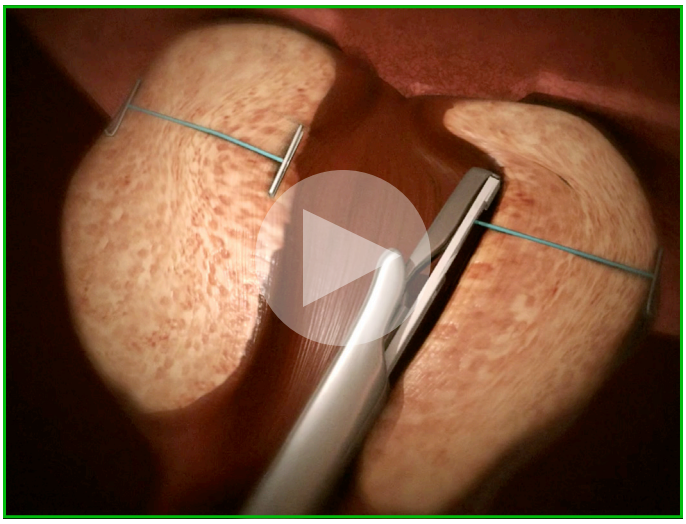


FIGURE 6 The UroLift implant and delivery device.

Source: Courtesy of NeoTract.



VIDEO 1

The UroLift System moves the obstructing prostatic tissue out of the way, opening the urethra. An implant holds the prostate in its new, less obstructed shape.

Click on image above or go to: https://www.urolifttforbph.com/urolift-animation.html

Source: Courtesy of NeoTract.

cadavers," recalled Makower. "The early results were very good with improvements in symptoms, improvements in urinary flow, and so on. We established that it was safe, relatively pain-free because we weren't cutting out the prostate or walloping it with energy or anything else that would mean a long and painful recovery period, and patients could get off the table and urinate easily. Having proven the clinical feasibility of the system, we were now ready to start a company." Makower, Lamson, and Catanese founded NeoTract and began product development for the UroLift device.

Developing the Solution

Following the team's clinical success in Australia, the team dove into a more formalized development effort to fine-tune the procedure and implant, as well as to develop a more sophisticated delivery device that could meet the need criteria in terms of utilizing a minimally invasive procedure rather than a surgical one (see Figure 6 and Video 2). The innovators filed numerous patents to secure broad coverage around their idea and began planning for an investigational device exemption to support the initiation of a large-scale U.S. trial in early 2007. "We were acutely aware of the problems caused by the lack of data accumulated by other BPH therapies," said Makower. "So our goal was to fund the company to do a really robust trial, recognizing that data was going to be critical for both reimbursement and for the success of the company."

However, even as the development of the device and early clinical studies advanced, the team hit an unexpected roadblock when the FDA went through a series of internal changes that effectively halted new investigational device studies. With their US clinical trial on indefinite hold, the NeoTract team made the strategic decision to go to Europe and pursue a CE Mark (the European equivalent of FDA approval to sell

a medical device commercially). With European approval in hand, the company could continue to advance the UroLift technology and begin to amass commercial experience, in parallel with its continued efforts to work through the delays in US market. According to Dave Amerson, a medical device executive with over 25 years of management experience with an emphasis in urology, who became NeoTract's CEO, "Europe provided some good insights that helped us further improve our product reliability, refine our surgeon training program, and strengthen our sales representative training."

By early 2011, NeoTract was finally able to begin enrolling the first patients in its 206 person, multinational randomized trial (LIFT). The results, published in May of 2013,[16] confirmed that the prostatic urethral lift (PUL) offered rapid and sustained mitigation of LUTS as measured by AUA-SI score improvements (17 percent improvement in first two weeks, 47 percent at six months, 51 percent at 1 year), and a clinically and statistically significant improvement in peak urinary flow rates (QMax). The study was designed such that all but one procedure conducted in North America were performed under true local anesthesia in the office or surgery center. Post-operative catheterization was 30 percent for an average duration of less than one day. Importantly, the LIFT study also reported that PUL offered the unique preservation of sexual function, which had the potential to differentiate UroLift in the treatment landscape. As the authors reported, "Stable erectile function and the absence of ejaculatory dysfunction suggest that this tissue sparing approach does not cause the adverse sexual function effects that accompany other BPH therapies."[17]

"Stable erectile function and the absence of ejaculatory dysfunction suggest that this tissue sparing approach does not cause the adverse sexual function effects that accompany other BPH therapies."

In terms of adverse events, the procedure was associated with minimal morbidity. Some patients experienced postoperative dysuria (34 percent), hematuria (25.7 percent), pelvic pain and discomfort (17.9 percent), and/or urgency (7.1 percent) that typically resolved within two weeks. (Patients receiving just a sham diagnostic cystoscopy experienced the same adverse effects, although at lower rates.) The study also found that if the implants were placed in a way that exposed them to bladder urine, encrustation could result. However, there were no such

issues with the implants when properly delivered within the prostate, which affirmed the need for surgeon training to ensure optimal implant placement.

The two-year data published on the LIFT study showed sustained improvements in symptoms, peak flow rate, and quality of life. The study cited a re-treatment rate of 7.5 percent at two years, which is only slightly above the expected re-treatment rate for TURP within that time frame. Patients that were re-treated underwent either additional UroLift implants or elected TURP or laser vaporization, all without complications.[18]

In September 2013, NeoTract received FDA de novo clearance to market UroLift in the US. And in November 2014, the company received Medicare reimbursement under two new CPT codes, effective January 2015. Although it is still too early to predict the extent to which UroLift will become a durable alternative between medical management and surgery in the treatment landscape for BPH, Amerson believes the technology has a good shot. "In my mind, to achieve category ownership, a technology has to do a number of things. First, it should do no harm/not burn any bridges, meaning that having the procedure doesn't prevent the utilization of other treatment strategies in the future. Second, it has to provide rapid relief. Third, it has to preserve the things that matter–in this case, urinary continence and sexual function. Fourth, it should be performable in multiple settings, in an office, ambulatory surgical center, or hospital. Finally, it should be easy to learn and provide durable, cost-effective results," he said. "NeoTract and the UroLift implant procedure meet all of those criteria."

GROUP DISCUSSION QUESTIONS

- Based on what is known from the case, how did Laserscope define the top-priority needs in BPH at the time it became interested in the space? In what ways did this affect the technology it developed and its positioning in the market?
- How did Laserscope's decisions pave the way for the next wave of innovators like NeoTract? Are NeoTract's clinical targets the right ones to potentially make a lasting change in established treatment paradigms?
- What new information about the treatment landscape are innovators and companies likely to act on in identifying new needs in BPH to address?

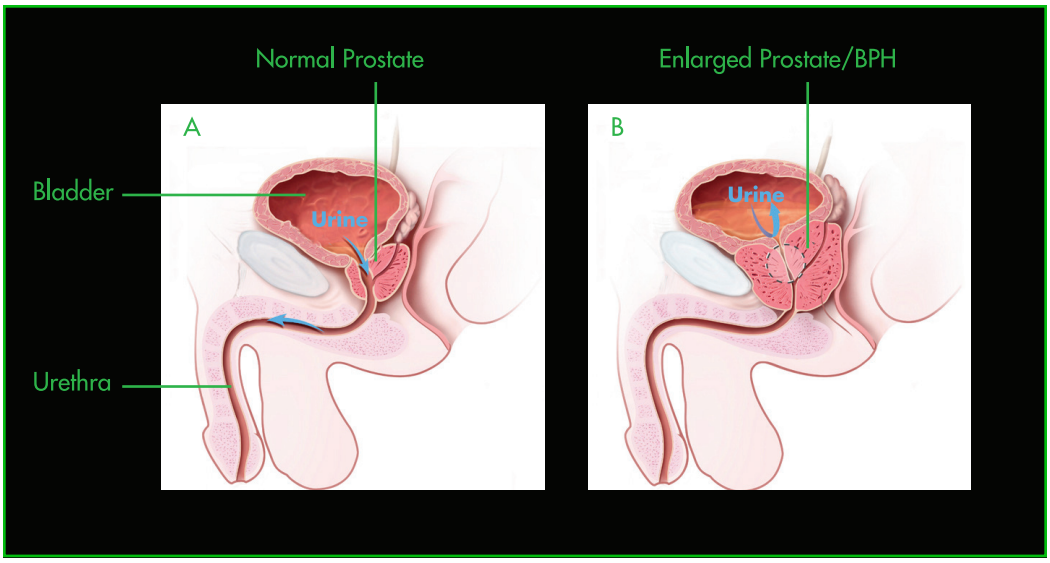
COMPANY (INTERNAL) DISCUSSION QUESTION

- What technology in your company's own portfolio could potentially benefit from a re-evaluation of the fundamental need (and how it may have evolved)?

FIGURE F1

When the prostate is of normal size (left), urine flows easily from the bladder through the urethra. When the prostate is enlarged (right), it presses in on the urethra and forces the bladder to work harder to expel urine.

Source: The website of the National Cancer Institute (www.cancer.gov).



BPH Feature

Background: Pathophysiology and Surgical Treatment of BPH

BPH occurs when the prostate gland, which sits just below the bladder and surrounds the urethra, becomes enlarged (see Figure F1). The prostate, which produces ejaculatory fluid, is made up of several lobes contained in an outer capsule. It is typically about the size of a walnut, but as men age, it can expand, causing the lobes on either side of the urethra to press inward and obstruct the flow of urine. Although considered a normal part of the aging process, these changes can produce bothersome lower urinary tract symptoms, such as increased urinary frequency, urgency, straining, and nocturia (frequent awakening to urinate during the night).[19] Additionally, BPH can lead to more serious complications, including acute or chronic urinary retention (inability to void), blood in the urine (hematuria) and urinary tract infections (UTIs), bladder or kidney damage, and bladder stones.[20] However, these outcomes are relatively uncommon unless the condition goes untreated for many years. More often than not, men are driven to seek treatment for BPH by the negative, ever-present impact that BPH has on their quality of life.

Treatment for BPH depends largely on the degree of bother experienced by the patient. A short questionnaire, the American Urological Association Symptom Index (AUA SI, also called the International Prostate Symptom Score or IPSS), is used to measure the severity of the symptoms and help doctors and patients evaluate treatment options and outcomes.[21] Mild symptoms are most often managed with "watch-

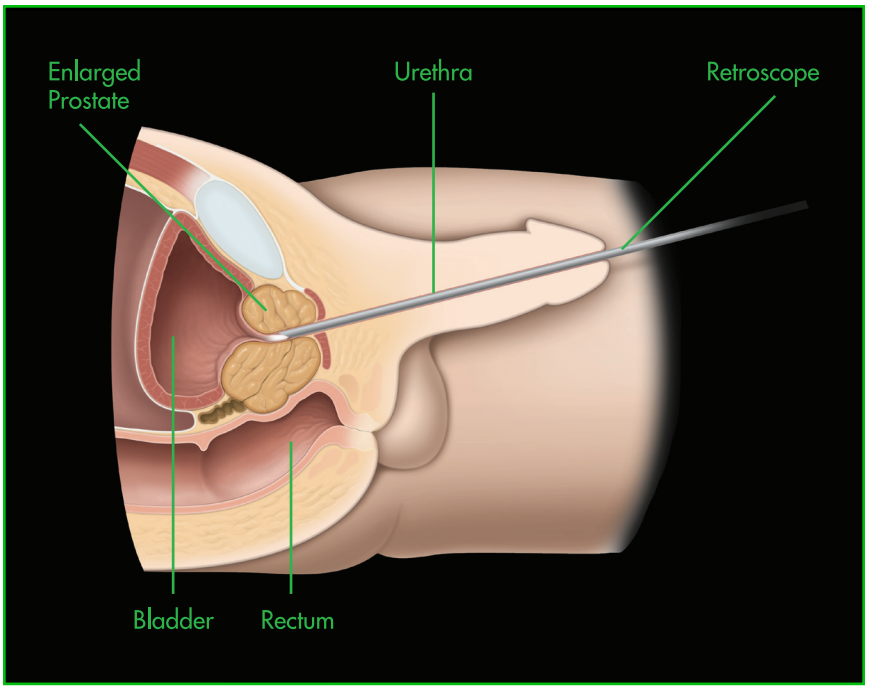


FIGURE F2

Surgery through the urethra.

Source: European Association of Urology, "EAU Patient Information on Benign Prostatic Enlargement," http://patients.uroweb.org (accessed November 2014)

ful waiting," which combines lifestyle changes (such as restricting fluids before bedtime and limiting diuretics like caffeine and alcohol) with regular check-ups, since BPH tends to progress.[22,23]

For moderate to severe BPH symptoms, the next line of therapy is medication. The two main drug treatments are alpha blockers, which work quickly to relax the smooth muscles of the prostate and bladder neck to improve urine flow, and 5-alpha reductase inhibitors, which take effect slowly but can prevent further prostate growth and may actually shrink the enlarged prostate. Combination therapy is also an option.[24] Unfortunately, these medications improve symptoms in only 30–60 percent of men[25] and may cause adverse side effects. For the alpha blockers, side effects can include headaches, dizziness, fatigue, and ejaculatory dysfunction in the form of retrograde ejaculation (wherein relaxed muscle tone precludes the normal closure of the bladder neck during ejaculation such that semen moves back into the bladder and is eliminated during urination instead of traveling out the penis) or anejaculation, where little or no semen is expelled from the prostate.[26] The possible side effects of 5-alpha reductase inhibitors are decreased libido, gynecomastia, erectile dysfunction, and ejaculatory dysfunction.[27] Both medications have to be taken daily, sometimes twice per day, on an indefinite basis. Because of undesirable side effects, non-response, or progression of the disease, roughly one-third of BPH patients discontinue medical therapy within one to two years.[28,29]

When medications are ineffective, obstructive symptoms become severe, or the patient experiences complications, the standard of care is an endoscopic surgical procedure to remove the inner part of the prostate (see Figures F2 and F3). The procedure, called transurethral resection of the prostate, or TURP, is performed at a hospital, usually under general anesthesia. TURP is considered the gold standard against which other BPH therapies are measured. In the procedure, the urol-

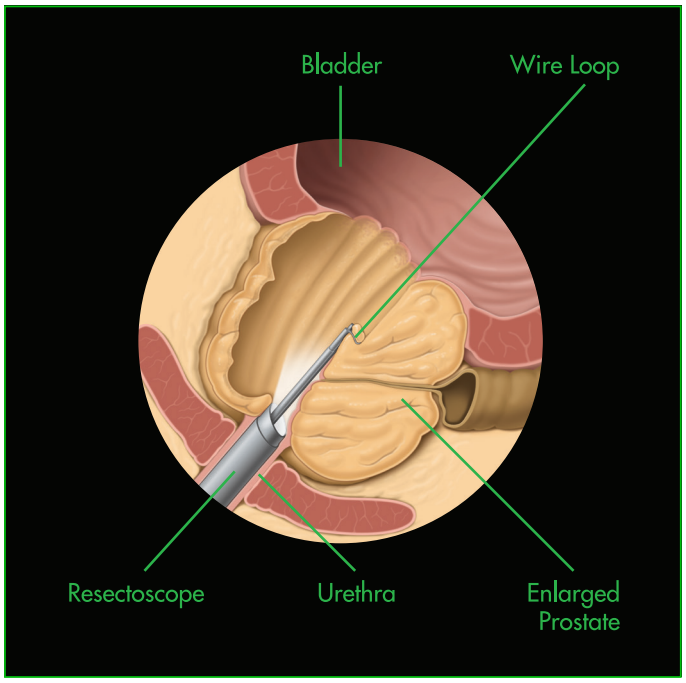


FIGURE F3

The resectoscope removes parts of the prostate tissue during TURP.

Source: European Association of Urology, "EAU Patient Information on Benign Prostatic Enlargement," http://patients.uroweb.org (accessed November 2014).

ogist inserts a resectoscope[30] through the tip of the penis into the urethra and uses an electrified wire loop to cut away a core of tissue inside of the prostate and cauterize blood vessels. A tiny camera allows the surgeon to see the operative field, while an irrigating fluid carries the chunks of tissue into the bladder, to be flushed out at the end. The patient typically stays in the hospital for one to three days, and has a urinary catheter in place during this time. Full recovery typically requires three weeks.[31]

While TURP is highly effective in relieving voiding symptoms, it has a high morbidity rate and risk of complications that include infection (15 percent), bleeding requiring a transfusion (5–10 percent), impotence (14 percent), retrograde ejaculation (73 percent), and urinary incontinence (1 percent). Another serious but rare complication is TUR syndrome, in which excess absorption of the electrolyte-free irrigating fluid used during the procedure causes a dangerous sodium imbalance in the patient. Later postoperative complications include scar tissue from the surgery that causes the narrowing of the urethra or the bladder neck (4 percent) and the need for additional surgery within five years (10 percent).[32]

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