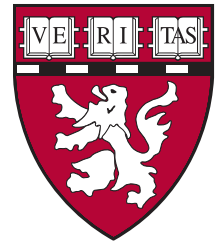


# Perspectives on PROSTATE DISEASE



HARVARD  
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How to handle a relapse: Your options if a PSA test reveals your cancer has returned

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a healthier life*

# Perspectives on Prostate Disease

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## Why this publication? Why now?

A message from Editor in Chief Marc B. Garnick, M.D.



Marc B. Garnick, M.D.

Few men think about their prostate gland until they develop some type of problem. Then it may be all they can think about.

If you have recently been diagnosed with prostate disease, you know how difficult it can be to find the in-depth and reliable information that will help you make informed treatment choices.

However, because of the health care system in this country, physicians and other health care providers often do not have adequate time to spend with patients. Typically, patient visits are scheduled every 15 to 30 minutes. In my practice, I may have a 60- to 90-minute initial consultation with a patient newly diagnosed with prostate cancer—but even that is often not enough time to truly get to know a man, what he values, and what concerns he, his family, and his significant other may have.

Patients are often forced to seek information elsewhere. Of course, brochures, newsletters, and Web sites about prostate disease abound. Unfortunately, most patient education brochures and primers offer only the basics, which are of little use to a man who's been dealing with prostate disease for several years—or who simply wants to know as much as possible, as soon as possible. The few in-depth Web sites and newsletters that exist typically provide information that is subtly (and sometimes not so subtly) biased in favor of one treatment over another, often because of commercial support. And the most important opinions and experiences of all—those of men who have actually been diagnosed with and treated for prostate disease—are somehow lost in the deluge of “professional” publications.

*Perspectives on Prostate Disease* was created to address these issues. Our mission in launching this quarterly newsletter is to provide multiple perspectives about how best to treat the most common prostate diseases—prostate cancer, benign prostatic hyperplasia, and prostatitis—as well as related conditions such as erectile dysfunction and low testosterone levels.

To ensure that we provide readers with the most accurate and objective information possible, the editorial content is devoid of any commercial bias. *Perspectives* is supported in part by a grant from a charitable nonprofit family foundation. It is published by Harvard Health Publications, the consumer health publishing division of Harvard Medical School. Our editorial board consists of eminent and respected Harvard and European physicians, all of whom have expertise in the disorders covered by *Perspectives*.

What can you expect when you read *Perspectives*?

- **Multiple perspectives.** We'll provide different perspectives, especially when discussing controversial issues such as the treatment of prostate cancer. Most men diagnosed with prostate cancer today learn they have the disease when it is at its earliest stages. Yet there is no consensus about how best to treat early-stage prostate cancer, and the side effects of various treatment options may be devastating. To better explore the controversies and options, we've included an overview article in this issue, as well as in-depth conversations with two men diagnosed with early-stage prostate cancer who made very different treatment choices.
- **Patients' stories.** Of course, the most important perspective is the patient's. You will notice in these pages that we have made a commitment to featuring prominently the stories of men diagnosed with prostate disease.
- **Expert opinions.** We plan to host periodic roundtable discussions among leading Harvard Medical School faculty, who will debate and analyze recent trends and practice in prostate disease and focus on real-life issues that come up in the daily practice of medicine. In these roundtable discussions, we'll capture the spontaneity of response rather than present well-prepared summaries of recent research, which are available elsewhere. Of course, the experts will emphasize current and emerging trends in treatments so that readers benefit from cutting-edge knowledge.
- **Research advances.** We round out *Perspectives* by evaluating the latest research published in the most credible medical journals or presented at scientific symposia, as well as treatment advances on the horizon. We also provide perspective on research and treatments from Europe and the rest of the world, when appropriate, because many advances originate outside the United States.

One personal comment: While my role in *Perspectives* is that of the physician editor in chief, as well as that of someone who has dedicated his life to the clinical care and research of prostate disease, I am also a patient who has been diagnosed with and treated for several of the prostate disorders discussed in this publication. In future issues, I will describe my personal experiences as a patient, getting and digesting medical advice. I have to admit, these experiences have changed my "perspective" quite a bit.

We look forward to fulfilling this pledge to you: *Perspectives* will bring you an unbiased, objective, and compassionate discussion of critical perspectives on prostate diseases, from the view of both Harvard doctors and the patients we serve.



Marc B. Garnick, M.D.

Editor in Chief, *Perspectives on Prostate Disease*

## Treat or wait?

Editor in Chief Marc B. Garnick, M.D., discusses issues and controversies about early-stage prostate cancer

Thanks to more widespread prostate-specific antigen (PSA) testing, today nine out of 10 men diagnosed with prostate cancer have tumors that are detected at the earliest stage, when they are still confined to the prostate gland and are so small they can be detected only through a biopsy.

Maybe you are one of these men. If so, it is likely that you are feeling overwhelmed by your diagnosis and all the treatment options for early-stage prostate cancer, and are wondering what to do next. You may even be feeling as though your life depends on making a treatment decision as quickly as possible. So it may surprise you to know that one respectable study indicates that you can take up to one year to evaluate the options before choosing a treatment, and it will not affect your long-term likelihood of remaining cancer-free (see “Time to decide,” below right).

Yet all too often when I meet with patients who are diagnosed with early-stage prostate cancer, I find that they want to rush into treatment without fully considering the ramifications of their decisions. What I often hear from patients who have just received a prostate cancer diagnosis are statements like “I want this out!” or “I just want to get on with my life.”

The emotional impact of cancer can be devastating—there’s no question of that. But you owe it to yourself to do whatever you need in order to remain calm and take things one step at a time. There is no one-size-fits-all treatment for early-stage prostate cancer (see “Two men, different choices,” page 4). Even the experts do not agree about which men with such cancers should be treated, which treatment method is best—or whether, for some tumors, any treatment is even necessary.

At the same time, every doctor knows that some men who undergo treatment for early-stage prostate cancer, and are considered “cured” on the basis of follow-up PSA tests, suffer relapse or “biochemical recurrence” (as measured by PSA levels) years later—indicating that the original cancer spread (metastasized) without being detected and has become active. What is going on? It is likely in these situations that individual cancer cells (micrometastases) shed from the tumor early on, but at levels too small to be detected by computed tomography or bone scans or by physical examination (see “Likelihood of progression,” page 4). Such micrometastases cause no symptoms initially but may do so in future months to years, as they grow into tumors. Research is under way to find better methods of detecting micrometastases (see “On the horizon,” page 10).

Complicating the matter still further, side effects of treatment can be

### Early-stage prostate cancer

Tumors with the following profile are considered early stage:

- Small tumor size (stage T2a or smaller)
- Low PSA (no more than 10 ng/ml)
- Low Gleason score (no more than 6)



### Time to decide

Researchers at Memorial Sloan-Kettering Cancer Center analyzed medical records of 3,149 men with early-stage prostate cancer who underwent a radical prostatectomy within a year of diagnosis. The time the men took to make a treatment decision did not affect likelihood of relapse (measured by a rising PSA level, known medically as a biochemical recurrence). This held true even for men at high risk for relapse, based on their clinical profile.

SOURCE: Boorjian SA, Bianco FJ, Scardino PT, Eastham JA. Does the Time from Biopsy to Surgery Affect Biochemical Recurrence after Radical Prostatectomy? *BJU International*, 2005;96:773–6. PMID: 16153197.

\* Whenever this icon appears, see “Searching PubMed in five easy steps,” page 48.

### Likelihood of progression

Investigators followed 81 men diagnosed with stage T1c prostate cancer for at least one year (some for nearly five years). The men underwent semiannual PSA tests and digital rectal exams and had annual prostate biopsies to see if the cancer had become active. At time of repeat biopsy, cancer had progressed in 25 men.

SOURCE: Carter HB, Walsh PC, Landis P, Epstein JI. Expectant Management of Nonpalpable Prostate Cancer with Curative Intent: Preliminary Results. *Journal of Urology* 2002;167:1231–4. PMID: 11832703.

 See p. 48.

### Two men, different choices

This issue of *Perspectives* profiles two patients who were diagnosed with early-stage prostate cancer and reached different conclusions about which strategy was right for them. See “Why one man opted for lifestyle changes instead of treatment,” page 15, and “Why one man chose robotic-assisted laparoscopic prostatectomy,” page 20.

devastating, destroying a man’s quality of life. For all these reasons, when I meet with patients, I encourage them to ask detailed questions and perform “due diligence” to ensure that they are making the right decisions about their medical care. Often used in a business context, the phrase “due diligence” means doing your homework, exploring all the options, and taking reasonable steps to protect yourself or someone else. When it comes to prostate cancer, due diligence begins with having the confidence to question your physician about treatment recommendations—after all, you are the person who has to live with the results.

### Why due diligence is important

When you receive a diagnosis of prostate cancer, you are inundated with information. Chances are you know the basics about your prostate gland (if not, see Figure 1 for a refresher) and your “numbers”—your PSA level, your Gleason score, and the stage of your cancer. Take the time to process this information, and ask for more details.

As you evaluate treatment options, I’d suggest that you think not only about your situation today, but also about where you expect to be in five or 10 years—because chances are, you’ll still be alive. And you need to be sure that you would make the same treatment decision five or 10 years from now as you will right now.

Will you be able to deal with impotence if it occurs? What about incontinence (which is actually the more devastating complication, if you ask most men dealing with it)? How will the possible side effects of treatment affect your relationship with your wife or significant other—and your very sense of self? It’s vital to really think about these issues: In my experience, truly informed patients are much better able to deal with adverse consequences than patients who are uninformed or rush into making a decision.

As you evaluate various treatment options, keep in mind that studies show that patients do not always mention problems such as incontinence or impotence to their doctors (see “Side effect reporting,” page 10). As a result, when your doctor cites numbers or percentages when trying to convey risk, the numbers may be on the low side. It’s not uncommon for a man to talk with other patients—at a support group or while searching for information—and to hear about higher proportions of people being affected by a particular problem (a subject to be covered in a future article in *Perspectives*).

It’s also important to understand the limits of current medical knowledge about prostate cancer, explored in the following pages.

### Diagnostic tests are limited

We always knew that prostate cancer is common and that, until recently, it often went undiagnosed: Autopsies of men who died of other causes have shown that about one-third of men over age 50 have some cancerous cells

in their prostate, while 90% of men over age 90 have such cells.

As PSA screening has grown more widespread, we are finding more tumors that otherwise would have escaped detection. Yet current diagnostic technology does not always enable urologists to determine which tumors will lie dormant and which will become active, spreading elsewhere in the body.

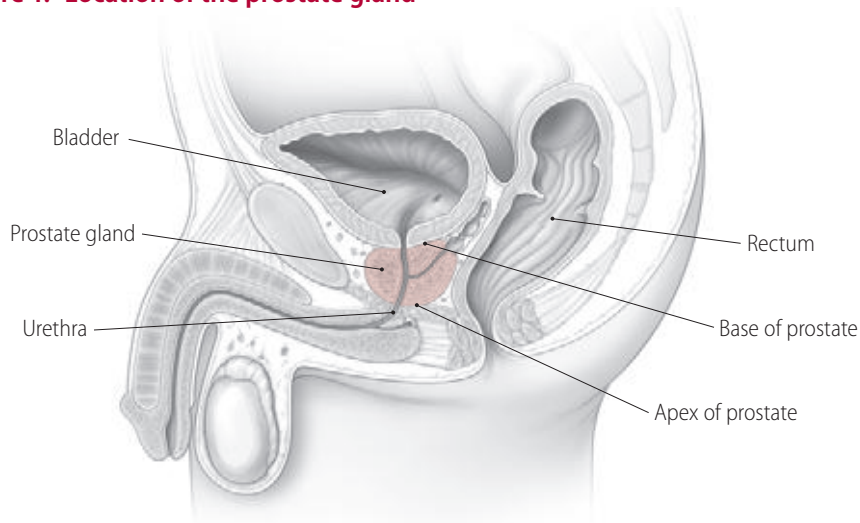
Studies estimate that anywhere from 16%–56% of men diagnosed with prostate cancer, generally because of an abnormal PSA test, have tumors that might never have caused problems had they not been found. And the landmark Prostate Cancer Prevention Trial (PCPT) unexpectedly yielded data that early-stage prostate tumors are incredibly common, even at PSA levels considered normal.

The PCPT was a randomized controlled study—the type considered to be the gold standard in research (see “Randomized controlled trials,” page 6). The study, which involved almost 19,000 healthy men, was designed to evaluate whether the drug finasteride (Proscar) could prevent prostate

### Conducting due diligence

For a step-by-step guide on how to conduct due diligence when evaluating treatment options for prostate cancer, see the complimentary insert accompanying this issue, “The guide to due diligence in early-stage prostate cancer.”

**Figure 1. Location of the prostate gland**



The prostate gland, about the size of a walnut, produces fluid that forms part of the semen that is ejaculated during sexual activity. The prostate is located adjacent to the rectum and just below the bladder, and wraps around the upper part of the urethra, which carries urine from the bladder out of the body.

This location creates challenges in both diagnosis and treatment. During a digital rectal exam, for example, a doctor is able to feel only the back portion of the prostate. If cancer has developed in the apex, base, or deep inside the prostate, it may not be palpable.

Surgeons and radiation oncologists also face challenges in eradicating a tumor without causing lasting damage to surrounding organs and structures. When removing a tumor from the breast or colon, a surgeon is able to remove enough surrounding tissue to ensure “clean margins,” meaning that all the cancer has been removed. But when treating prostate cancer, a comparable amount of tissue cannot be removed surgically or targeted. It takes a skilled surgeon and radiation oncologist to eradicate diseased tissue without harming portions of the rectum, bladder, and penis, thereby minimizing the likelihood of complications.

## Randomized controlled trials

In randomized controlled studies to determine a drug's effectiveness, physicians randomly assign participants to either take the medication under investigation or join a control group whose members receive a placebo. In this way, physicians eliminate biases in both the selection of patients and interpretation of data that might otherwise lead them to conclude the treatment was more effective than it would be in a random collection of people.

cancer from developing. Finasteride is a hormonal medication originally approved to treat benign prostatic hyperplasia (an enlarged prostate, which can cause problems with urination), but which has also been investigated as a potential treatment for prostate cancer.

All participants were ages 55 and older with PSA levels of no more than 3.0 nanograms per milliliter (ng/ml) and normal digital rectal exams—in other words, by the traditional testing standards, they showed no evidence of prostate cancer. Investigators randomly assigned participants to take finasteride or a placebo, and the men were followed for seven years. Every year, all participants underwent a digital rectal exam and had their PSA levels tested.

Every participant in the PCPT also agreed to undergo a prostate biopsy at the end of the study, whether he met the clinical criteria for such a biopsy or not. The reason investigators included this requirement was that they wanted to eliminate any “detection bias,” a technical term for unintended differences in diagnosis between comparison groups in a study—in this case, between the men randomly assigned to finasteride and those assigned to receive placebo.

At the end of seven years, investigators found that finasteride reduced the risk of developing prostate cancer by almost 25%. But they also found that the men taking finasteride who did develop prostate cancer were more likely to develop high-grade tumors and experience sexual dysfunction than the men taking placebo. (Future issues of *Perspectives* will explore the PCPT in greater detail.)

One aspect of the PCPT did not generate a lot of media attention, but sheds significant light on decisions about whether and how to treat early-stage prostate cancer. Of the 18,882 men enrolled in the study, 9,459 received a placebo. Of these men, 2,950 never had PSA levels greater than 4.0 ng/ml or abnormal digital rectal examinations—and so, normally, they would never have undergone a prostate biopsy. By all indications, they should have been cancer-free.

But when these supposedly healthy men underwent biopsies as a requirement of the study, investigators found something surprising: A significant number actually had cancer that otherwise would have gone undetected. And of the men who developed such tumors, high-grade cancers (those considered significant) were found even at the lowest detectable PSA levels (see Table 1).

This study inadvertently provided evidence not only that prostate cancer occurs more often than once believed, but also that PSA levels may not be a reliable indicator of which cancers are most aggressive. Both findings add weight to the growing consensus that many prostate tumors currently being detected may not need to have been diagnosed or treated in the first place.

## Cancer staging may miss errant cells

Once a pathologist confirms that cancer is present, the doctor will next determine how far the cancer extends—a process known as cancer staging—

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## For more information

To learn more about the PCPT:

Thompson IM, Goodman PJ, Tangen CM, et al. The Influence of Finasteride on the Development of Prostate Cancer. *New England Journal of Medicine* 2003; 349:215–24. PMID: 12824459.

Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level  $\leq 4.0$  ng per Milliliter. *New England Journal of Medicine* 2004; 350:2239–46. PMID: 15163773.

 See p. 48.

and discuss the implications with you. This is perhaps the most important information of all for you to obtain, as it determines whether the cancer is likely to be curable, or whether it has already spread to additional tissues, making prognosis much worse.

If you were my patient, I would ask you to consider two important points. First, cancer staging actually occurs in two phases: clinical (based on information obtained preoperatively) and pathological (based on information obtained during surgery). Of the two, pathological staging is more accurate.

A second point to understand, however, is that even pathological staging can be inaccurate (see Figure 2). A cancer spreads, or metastasizes, once a primary tumor sheds cancer cells that travel elsewhere in the body and establish other tumor sites. Metastasis is a complex process that researchers do not fully understand. What is clear is that this process involves multiple genetic mutations and steps, and that each type of cancer spreads in a unique way.

Individual prostate cancer cells can spread to more remote areas of the body in three ways (see “How prostate cancer spreads,” at right). What’s more, they can do so without being detected with our current technology, essentially escaping “under the radar.” So it’s always possible—even if you are diagnosed with early-stage prostate cancer—that the cancer has already spread and will manifest in the coming years. How likely is it that an early-stage prostate cancer will become active without treatment? A small study provides some clues (see “Likelihood of progression,” page 4).

**How prostate cancer spreads**

- The cells escape into the bloodstream, initially by invading small blood vessels around the tumor, then traveling to larger blood vessels that enable the cells to circulate around the body (a situation known as vascular invasion).
- The cells are filtered through the body’s lymph system; although some are captured in lymph nodes, others may travel elsewhere in the body.
- The cells migrate along the length of a nerve, escaping from the prostate into adjacent soft tissue (a situation known as perineural invasion).

**Table 1. Why a low PSA does not mean you are “cancer-free”**

The Prostate Cancer Prevention Trial included a provision that men randomized to receive placebo undergo a prostate biopsy at the end of the study, even if they had normal PSA levels and digital rectal exams. To their surprise, investigators found that many of these men had prostate cancer—in some cases, high-grade prostate cancer.

PSA level	Number of men (2,950 total)	Men with prostate cancer	Men with prostate cancer whose tumors were high grade (Gleason score 7 or more)
up to 0.5 ng/ml	486	32 (6.6%)	4 (12.5%)
0.6–1.0 ng/ml	791	80 (10.1%)	8 (10.0%)
1.1–2.0 ng/ml	998	170 (17.0%)	20 (11.8%)
2.1–3.0 ng/ml	482	115 (23.9%)	22 (19.1%)
3.1–4.0* ng/ml	193	52 (26.9%)	13 (25.0%)

\*NOTE: A PSA level over 4.0 ng/ml traditionally triggers a biopsy.

*Adapted with permission from I.M. Thompson, et al. Prevalence of Prostate Cancer Among Men with a Prostate-Specific Antigen Level ≤4.0 ng per Milliliter. New England Journal of Medicine, May 27, 2004, Table 2.*

### Treatments may have side effects

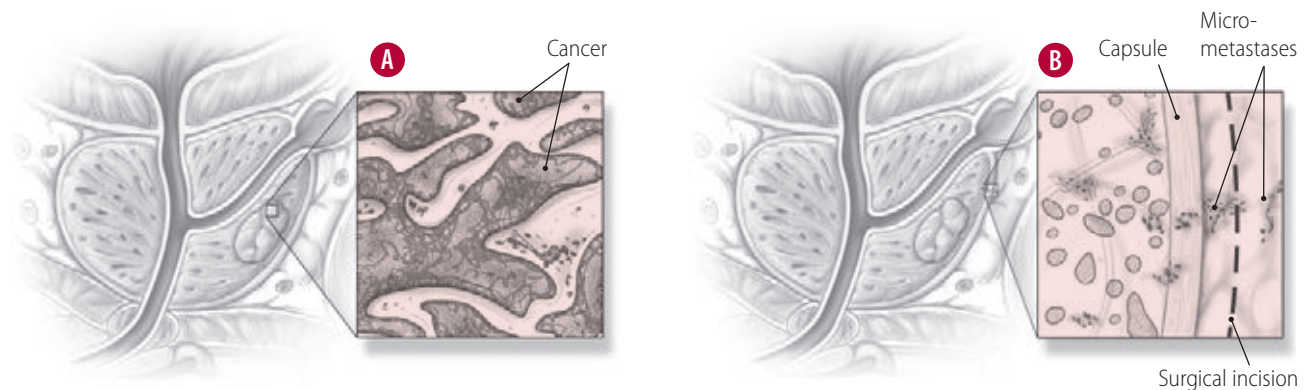
The treatment options for early-stage prostate cancer fall into three broad categories: surgery, radiation therapy, and active surveillance. Your doctor will make a treatment recommendation based on your “numbers” as well as a mathematical tool known as a nomogram, which can help you and your doctor better assess how extensive your cancer is likely to be and whether it is likely to become active in the future.

Yet clinical studies have not provided any evidence that one treatment is better than another—or that any treatment at all actually prolongs life: The average 5-, 10-, and 15-year survival rates are virtually the same for all treatment options in early-stage prostate cancer, including active surveillance. It’s also important to understand that no mathematical model is foolproof, and some men diagnosed with early-stage, locally confined disease will later find out that their cancer was more extensive than originally believed.

If you are diagnosed with early-stage prostate cancer, you have a number of treatments to choose from. Future issues of *Perspectives* will explore these options in greater detail. For now, a brief comparison is listed in Table 2.

**Radical prostatectomy (surgery).** The surgeon removes the prostate and seminal vesicles (saclike glands that release fluid that becomes part of semen). In some cases, pelvic lymph nodes are also sampled. This is most often performed through an abdominal incision; abdominal surgery may also be done with a laparoscope. A third option is the perineal technique, involving an incision in the area between the scrotum and the anus (the perineum).

**Figure 2. Why understaging may occur**



When the prostate is removed, a pathologist examines slices of the gland for evidence of cancer. **A.** Under a microscope, the pathologist can distinguish tiny tumors, consisting of clumps of visibly abnormal cells. **B.** With current imaging technology, it is not yet possible for a pathologist to identify micrometastases—individual cancer cells shed from the primary tumor—that have gone on to seed adjacent tissue. In this image, for example, cancer cells have already penetrated the capsule and migrated to adjacent tissue, even beyond the margin of tissue removed during surgery.

**Table 2. What guides treatment recommendations**

Both of the situations below involve men diagnosed with a tumor that is small in size (stage T2a or smaller), yet who may require quite different treatments, based on their PSA level and Gleason score. Of course, many men have clinical profiles that vary from these two extremes.

Clinical profile	Probable pathological stage	Treatment recommendation
Low PSA (less than 10 ng/ml) Low Gleason score (no more than 6)	80% of men with this profile probably have locally confined disease.  It is likely that fewer than 3% will have evidence of cancer in lymph nodes.	Surgery, radiation, or active surveillance (depending on exact clinical profile).
High PSA (more than 20 ng/ml) High Gleason score (8–10)	5% of men with this profile probably have locally confined disease.  More than 20% probably have evidence of cancer in the lymph nodes.	Systemic therapy rather than surgery (may involve some combination of hormonal and radiation therapy).

The most common side effects are

- impotence (affecting 30%–70% of men)
- mild to severe incontinence (2%–15%).

**External beam radiation therapy.** After a CT scan constructs a three-dimensional picture of the prostate and seminal vesicles, the radiation oncologist directs rays of high-energy radiation at the prostate tumor and sometimes at nearby lymph nodes. The most common side effects are

- impotence (30%–70%)
- mild to severe incontinence (1%–2%).

**Brachytherapy.** With ultrasound guidance, radioactive “seeds” or pellets are implanted in the prostate itself to irradiate the tumor. The most common side effects are

- impotence (30%–50%)
- mild to severe incontinence (2%).

**Active surveillance.** This involves an extended period of monitoring the cancer with regular digital rectal exams, PSA tests, and sometimes repeated prostate biopsies. If tests indicate cancer has become active, treatment options are offered. The major risk of active surveillance is that the cancer could become active during the period of surveillance, potentially making prognosis worse.

### Side effect reporting

When thinking about side effects, it's important to understand that patients don't always talk openly with their doctors about the impact treatment has had on their quality of life—or sometimes, doctors don't ask. The following studies are just a sampling of the patient-reported data that have been published, which may provide a more accurate assessment of side effects.

**Fecal incontinence.** A telephone survey of 227 men with prostate cancer revealed that 5% of those who underwent radical prostatectomy and 18% of those who had a perineal prostatectomy developed fecal incontinence afterward. Yet fewer than 50% told their physicians. (Source: Bishoff JT, Motley G, Optenberg SA, et al. Incidence of Fecal and Urinary Incontinence Following Radical Perineal and Retropubic Prostatectomy in a National Population. *Journal of Urology* 1998;160:454–8. PMID: 9679897.)

**Erectile dysfunction.** A mailed questionnaire returned by 1,236 men with localized prostate cancer who had undergone either prostatectomy or radiation therapy revealed that 36% had erectile dysfunction at the time of diagnosis. Yet when contacted an average of four years after treatment, more than twice as many men (85%) said they had erectile dysfunction. Only 13% were able to have firm, reliable erections spontaneously. Respondents indicated that they were as concerned about the loss of sexual desire and the ability to have an orgasm as they were about erectile dysfunction. (Source: Schover LR, Fouladi RT, Warneke CL, et al. Defining Sexual Outcomes after Treatment for Localized Prostate Carcinoma. *Cancer* 2002;95:1773–85. PMID: 12365027.)

**Urinary incontinence.** A retrospective analysis based on Medicare claims submitted by 11,522 men who underwent prostatectomy for prostate cancer found that more than one year after surgery, 18%–24% (the proportion increased with age) had suffered symptoms of urinary incontinence or had undergone procedures to correct urinary difficulties. (Source: Begg CB, Riedel ER, Bach PB, et al. Variations in Morbidity after Radical Prostatectomy. *New England Journal of Medicine* 2002;346:1138–44. PMID: 11948274.)

**Rectal cancer risk.** A retrospective analysis of the outcomes of 30,552 men who received radiation for prostate cancer found that they were almost twice as likely to develop rectal cancer as a comparison group of 55,263 men who treated their cancer with surgery. (Source: Baxter NN, Tepper JE, Durham SB, et al. Increased Risk of Rectal Cancer after Prostate Radiation: A Population-Based Study. *Gastroenterology* 2005;128:819–24. PMID: 15825064.)

### On the horizon

Given the current limits in diagnosis, prognosis, and treatment, research advances become even more important. Here's a brief look at other diagnostic and prognostic tests currently in development.

### Prostate cancer “fingerprints”

New types of genetic diagnostic technology, known as gene chips or genetic microarrays, use computers to analyze the activity of hundreds and sometimes thousands of genes at a time. The tests can reveal certain telltale patterns that indicate whether inborn controls that inhibit cancer growth—such as controls of blood vessel growth (angiogenesis), cell differentiation and proliferation, and cell adhesion—remain in place or have failed. Think of these patterns as molecular fingerprints that help researchers identify which are the most aggressive cancers and therefore are most likely to spread. The technology is already commercially available for use in breast cancer. Several gene chips for prostate cancer are in development and are expected to reach the market within five years.

### Autoantibody signatures

Other researchers are investigating whether it is possible to analyze blood samples for the presence of particular antibodies, immune system chemicals that attack cancer cells and other abnormal cells. One study published in the *New England Journal of Medicine* found that a computerized microarray device could use antibody detection to identify people with prostate cancer more accurately than a PSA test. Although more research has to be done, the hope is that antibody analysis will enable doctors to detect cancer at its earliest stages, when your own immune system has identified the abnormal growth and is trying to suppress it. (Source: Wang X, Yu J, Sreekumar A, et al. Autoantibody Signatures in Prostate Cancer. *New England Journal of Medicine* 2005;353:1224–35. PMID: 16177248.) ♥

## When to consider active surveillance

### Which men are candidates for delaying prostate cancer treatment?

Increasing evidence suggests that men at low risk for cancer progression—including many of those with small tumors detected only through PSA screening—should consider a strategy of active surveillance rather than treatment. If you have just been diagnosed with early-stage prostate cancer and are debating the options, should you consider active surveillance?

The studies have produced mixed results, as explained in more detail below. But a 2005 review in the *Journal of Oncology* proposed a set of guidelines that may be helpful in designing a strategy of active surveillance. Table 3 outlines the suggested parameters.

#### What the studies say

Clinical studies have been mixed about the health outcomes of men with early prostate cancer who adopt a strategy of active surveillance, as compared with men who choose other strategies. Unfortunately, this only further muddies the waters and makes it hard to provide clear guidelines for treatment. Several notable studies and their results are summarized below. (To find the studies themselves, see “For more information” at left and on facing page.) Further studies are under way that may help clarify whether it’s wise to opt for active surveillance.

#### The Scandinavian study

This study followed 223 men with early-stage cancer who did not seek treatment. At a 15-year follow-up, the men had health outcomes similar to a control group of men without prostate cancer. However, at a subsequent follow-up, researchers found that the men were more likely than the control group to die of prostate cancer 15–20 years after initial diagnosis.

#### The Connecticut Tumor Registry study

This study involved 767 men diagnosed with early-stage prostate cancer who either were not treated or underwent hormone therapy (not considered curative). Researchers found that men whose Gleason scores were between 2 and 4 were less likely to die of prostate cancer within 15 years—and even afterward—than those with higher Gleason scores.

#### The intensive lifestyle change study

This study involved 93 men diagnosed with early-stage prostate cancer who decided to forgo treatment; the men were randomly assigned to adopt lifestyle changes or to a control group. (The lifestyle changes included a vegan

#### For more information

**Scandinavian study:** Johansson JE, Andren O, Andersson SO, et al. Natural History of Early, Localized Prostate Cancer. *Journal of the American Medical Association* 2004;291:2713–9. PMID: 15187052.

**Connecticut Tumor Registry study:** Albertsen PC, Hanley JA, Fine J. 20-year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer. *Journal of the American Medical Association* 2005;293:2095–2101. PMID: 15870412.

**Intensive lifestyle change study:** Ornish D, Weidner G, Fair WR, et al. Intensive Lifestyle Changes May Affect the Progression of Prostate Cancer. *Journal of Urology* 2005;174:1065–70. PMID: 16094059.

 See p. 48.

diet supplemented by vitamins and nutrients, regular exercise, stress reduction, and support group attendance.) Although the study did not look at survival, it did find that men who made lifestyle changes saw their PSA levels decrease by 4%, while PSA levels in men in the control group increased by 6%—a rough indicator of disease activity.

### The Scandinavian Prostate Cancer Group study

Another Scandinavian study compared the long-term outcomes of radical prostatectomy with active surveillance. The study randomly assigned 695 men with early-stage prostate cancer to receive either surgery or active monitoring. Over all, surgery increased the chances of survival. By the time eight years had passed, for example, 8.6% of men who underwent surgery had died, compared to 14% of those involved in active surveillance. Although it is not clear whether the results are applicable to men whose cancers are detected through screening, this study has caused experts to urge caution when it comes to forgoing treatment.

### The active surveillance algorithm study

Researchers at the University of Toronto developed a treatment algorithm in an effort to better differentiate men diagnosed with early-stage prostate cancer who can continue active surveillance from those who require intervention. The researchers used an algorithm that combined PSA doubling-time estimates and the results of follow-up biopsies (done 1, 4, 7, and 10 years after diagnosis) to determine whether treatment was necessary. The study involved 299 men diagnosed with localized prostate cancer who have been followed for eight years so far (the study is ongoing).

Most patients in the study (65%) continue active surveillance. Over all, 85% of the men remain alive, and most who have died succumbed to other causes; only 2 of the 299 have died of prostate cancer (a 99.3% disease-specific survival rate). The authors therefore propose that the combination of PSA monitoring and repeat biopsies may provide a way to determine who can continue active surveillance and who requires treatment. (For the algorithm, see Table 3.)

### Benefits and risks of active surveillance

The chief benefit of active surveillance is that it allows you to avoid the possible side effects of treatment for early-stage prostate cancer. Some men also welcome the opportunity to buy time, as they wait for improved methods of detection or new treatment options.

The most significant risk of active surveillance is that your cancer was understaged—in spite of improved estimates made possible by mathematical calculations of risk, known as nomograms—and that without treatment it will continue growing and possibly even spread. In fact, probably one in four men who decide to opt for active surveillance will be advised to undergo

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### For more information

**Scandinavian Prostate Cancer Group study:** Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical Prostatectomy Versus Watchful Waiting in Early Prostate Cancer. *New England Journal of Medicine* 2005;352:1977–84. PMID: 15888698.

**Active surveillance algorithm study:** Klotz L. Active Surveillance with Selective Delayed Intervention for Favorable Risk Prostate Cancer. *Urological Oncology* 2006;24:46–50. PMID: 16414494.

 See p. 48.

treatment at some point during the surveillance period, on the basis of either PSA doubling or an increased Gleason score.

You should therefore consider the emotional and personal aspects of active surveillance. If you think you are likely to grow unduly anxious at the thought that cancer might be growing inside you, this strategy is not for you. On the other hand, if you are comfortable with the best mathematical predictions of risk we have available, and with monitoring your cancer through regular tests and biopsies, then this strategy may be the right choice.

It's important to understand that active surveillance is just that—it requires multiple follow-up visits to your doctor, as well as multiple tests. As indicated in Table 3, if you choose active surveillance, you will undergo frequent PSA testing and digital rectal exams, as well as repeat prostate biopsies.

On the other hand, medical technology is improving all the time, and you may soon have additional information to help you monitor your situation. In the next five years, for example, DNA microarray technology may make it possible for doctors to take a blood sample and analyze patterns in multiple genes to better assess the risk of your tumor's growing and progressing (see "On the horizon," page 10).

For now, though, do yourself a favor if you are diagnosed with early-stage prostate cancer: At least discuss the possibility of active surveillance with your doctor. This is an option that deserves more attention. And if you decide to pursue treatment, carefully review all the options and risks. ♥

<b>Table 3. Proposed guidelines for active surveillance</b>
<b>Eligibility guidelines</b>
<ul style="list-style-type: none"> <li>• PSA no higher than 10 ng/ml</li> <li>• Gleason score no higher than 6</li> <li>• Tumor stage T1c to T2a</li> <li>• Life expectancy more than 15 years</li> <li>• Prostate biopsy finds cancer in no more than two core samples, and cancerous cells are present in less than half of each core</li> </ul>
<b>Monitoring guidelines</b>
<ul style="list-style-type: none"> <li>• PSA test and digital rectal exam every three months for two years; if PSA level remains stable, every six months thereafter</li> <li>• Prostate biopsy (10–12 core samples) at one year; if no cancer, repeat biopsies every three years until age 80</li> </ul>
<b>Treatment should occur when</b>
<ul style="list-style-type: none"> <li>• PSA level doubles in less than three years, on basis of eight PSA tests</li> <li>• Gleason score increases (7 or more)</li> </ul>
<i>Adapted with permission from Klotz L. Active Surveillance for Prostate Cancer: For Whom? Journal of Clinical Oncology 2005;23:8165–9, Table 2.</i>

## A patient's story:

### Why one man opted for lifestyle changes instead of treatment

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Ben Hunter, 64 years old, works as a film writer and director and is actively involved in various philanthropies. Ten years ago, he was much like any other man in his mid-50s: He was married with children, felt generally healthy, and had no real urinary difficulties. He tried to exercise when he could and ate a typical American diet.

After spending two years in California, where he was working on a film, Ben returned to his home on the East Coast in 1996. He contacted his doctor to schedule a routine physical exam. But his routine was about to be disrupted.

While doing a digital rectal exam, Ben's internist felt something on his prostate gland that she described as an "anomaly"—not entirely normal, but not suggestive of cancer, either. She recommended a PSA test, which revealed that Ben's PSA was 5.7. Ben subsequently underwent a prostate biopsy. One of the cores removed during the biopsy contained cancer. The Gleason score was 3+3. Ben underwent a bone scan and a computed tomography scan, but there was no evidence of metastases.

Ben sought advice from several doctors and did a great deal of research on his own. Almost every physician Ben consulted with suggested that he undergo traditional treatment with either a radical prostatectomy or some form of radiation therapy. After giving the matter much thought and doing extensive research, Ben instead decided on a strategy of active surveillance. In this interview, he explains why.

*Can you share some of the emotions and thoughts you had while dealing with your diagnosis?*

You know, before I had prostate cancer I didn't even know I had a prostate gland. So I went from a base of not even knowing that this gland existed to finding out I had cancer in it. At first, I was fearful. I couldn't sleep at night. I was worried about the future.

*What type of research did you do, as you evaluated treatment options? And what information most affected your decision?*

I started to gather information and seek out other opinions about what I should do. I consulted with at least three physicians. What amazed me was that there were many choices, but no clear indication of which was best. I could choose from radical prostatectomy, traditional radiation, radioactive seeds, freezing the prostate, burning the prostate—there were all these differ-

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*Editor's note: To maintain his privacy, Ben's name has been changed. All other details are as reported.*

ent options. The doctors presented the pros and cons of each one and recommended that I think about it carefully and then decide what I wanted to do.

Nobody rushed me. The doctors all said this was a slow-growing cancer and that I could take a month or two to investigate and decide which way to go. But nobody suggested the option of active surveillance. At the time, that type of strategy was normally reserved for people who were a lot older than I was, or people who had some other serious medical condition that would make treatment too risky.

As it happens, my wife does occasional research about medical conditions for friends. So she helped me do research on the Internet as well as in books, to learn more about the disease so that I could try to make a treatment decision.

And what bothered me was that, literally in the first month that I was thinking about this, I started to hear anecdotes about other men in my position. I heard about one acquaintance who had surgery for prostate cancer, suffered adverse consequences, and then his cancer had come back. So that made me wonder how effective the treatments were. Those anecdotal pieces of evidence were very profound, because you'd think, "Wow, what if that happened to me? That would be a terrible outcome." So I decided to really research and think things through carefully before doing anything.

*It sounds as if the side effects of treatment were most bothersome to you, and might have had the most impact on your decision. Is that accurate?*

I know some men with prostate cancer think, "Do whatever it takes to cure me of this disease." For me, it was more a matter of weighing the risks and benefits.

At the time, what most hit me were the side effects of treatment. The doctors told me that with surgery there was a 30% chance of impotence, and maybe a 5% chance of incontinence. That's a pretty stunning thing to hear, when you consider yourself in the prime of life and healthy. But radiation wasn't any better. It had similar complications, with slightly different percentages, but it might also cause rectal damage. So I continued to research the various options and compare the numbers.

It became clear that the various treatments had slightly different side effect profiles, but not meaningfully different. So then it became a question of, if I'm going to face these side effects, what are the chances that a treatment will actually improve my health or my longevity? And what I found out was that there was no information that proved that any of these treatments would actually lengthen my life. So that really struck me. It was all risk and no guarantee of benefit.

*You've made some significant lifestyle changes. Can you talk about why you thought this was so important?*

From my research, I knew that in Japan, prostate cancer was very rare. I came across an autopsy study comparing men who died in auto accidents in either

### Treatment side effects

For current estimates of side effects for surgery and radiation, see "Treatments may have side effects," page 8.

Japan or the United States. It found that the number of precancerous prostate lesions was about the same in both groups. And yet the prevalence of prostate tumors is much higher in America than it is in Japan (see Figure 3). But when Japanese men move to America, after a generation or two, their prostate cancer rates are the same as American men. So this led me to hypothesize that prostate cancer is a lifestyle disease.

This raised the possibility that if I could change my lifestyle, then perhaps I could combat the disease. An important part of my thinking was the fact that all the doctors I talked to agreed that prostate cancer, for most men, is a slow-growing disease. So I saw lifestyle change as a two-prong strategy: It might inhibit new tumors from emerging, while slowing the growth of existing tumors.

The slow-growing nature of these tumors also meant that there was always the chance that I would die from another disease or accident without facing the terrible side effects from prostate cancer treatment. And new medical or nonmedical treatments might emerge, such as a cancer vaccine. So in some ways I decided to play for time.

The final piece in my decision-making process was that I had an alternative: making lifestyle changes. I did some reading, and I went on the Internet and saw what people were posting in online support groups. I accumulated information slowly. In the end, I made about 50 lifestyle changes in response to having cancer.

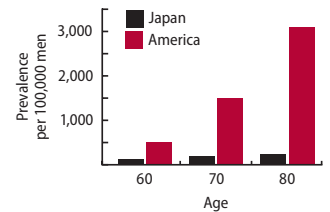
#### *What dietary changes did you make?*

I am now a vegetarian. I eat a lot of fruits and vegetables. I try to eat food that is as close to the source as possible, such as whole grains. First I followed a macrobiotic diet. But then I modified that diet as I read about additional studies. For instance, one study came out of Harvard about the benefit of eating cooked tomatoes, which reduces the risk of prostate cancer (see “Tomatoes and prostate cancer risk,” page 18). So now I eat seven to 10 servings of cooked tomatoes per week in foods like spaghetti sauce and so on. For the past decade I have not eaten any kind of animal meat whatsoever. But I usually eat fish twice a week, for the omega-3 fats, which laboratory studies have shown may slow tumor growth. Each day, I drink one glass of red wine and have at least three cups of green tea—for the antioxidants, which limit cell damage.

I don't eat dairy products or eggs. I've had almost no refined sugar in the past decade—not one single piece of cake or pie, not one doughnut, not one cupcake. For the past five years, I've had about one oatmeal raisin cookie a month, as an occasional indulgence.

One good thing about this diet: I've lost at least 10 pounds. And that's important because I learned early on that keeping my weight down might protect against the development and progression of cancer.

**Figure 3. Prostate cancer risk varies by country**



Various studies indicate that by age 60, American men are more likely to develop clinically detectable prostate tumors than are Japanese men, even though autopsy studies indicate that until age 50, microscopic prostate cancer cells are found in a similar percentage of American and Japanese men.

SOURCE: *Journal of Urology*, April 1990.

#### **Macrobiotic diet**

As much a philosophy as a diet, macrobiotic eating emphasizes organically grown fruits, vegetables, and whole grains, as well as food choices that contribute to health and internal balance.

## Tomatoes and prostate cancer risk

A number of studies have concluded that eating tomatoes may reduce risk of prostate cancer. It remains unclear whether lycopene or some other nutrient in tomatoes is responsible.

SOURCES: Kristal AR. Vitamin A, Retinoids, and Carotenoids as Chemopreventive Agents for Prostate Cancer. *Journal of Urology* 2004;171:554–8. PMID: 14713755.

Miller EC, Giovannucci E, Erdman JW, et al. Tomato Products, Lycopene, and Prostate Cancer Risk. *Urology Clinics of North America* 2002;29:83–93. PMID: 12109359.

 See p. 48.

## COX-2 inhibitors

Evidence suggests that regular use of NSAIDs and COX-2 inhibitors may reduce the risk of developing prostate cancer. But more research is necessary before doctors will be ready to recommend this strategy. It's also important to remember that regular use of NSAIDs and COX-2 inhibitors has been linked to cardiovascular and kidney problems, so weigh all the health benefits and risks.

SOURCE: Basler JW and Piazza GA. Nonsteroidal Anti-Inflammatory Drugs and Cyclooxygenase-2 Selective Inhibitors for Prostate Cancer Chemoprevention. *Journal of Urology* 2004;171:559–62. PMID: 14713756.

 See p. 48.

*What other sorts of changes have you made in your lifestyle?*

I work on stress reduction. I now do yoga and go for massage therapy. I exercise about four times a week. And I try to take time to “smell the flowers,” as they say, and take walks in the woods.

I also take a COX-2 inhibitor, Celebrex, every day, because it may be helpful in keeping the cancer at bay (see “COX-2 inhibitors,” below left). And I take quite a few supplements every day, based on what I've studied on the Internet and in books. For example, I take B-complex vitamins and saw palmetto. In 1999, I went to a doctor who specializes in integrative medicine, who's helped me modify some of the things that I take.

At one point, I took PC-SPES, a Chinese herbal remedy. This was actually recommended by a urologist at a hospital in New York who was being treated for colon cancer and was taking a similar compound, called SPES. I started taking a version for prostate cancer, PC-SPES, and it was very effective in lowering my PSA levels. But at the doses I was taking, it was mentally debilitating. So eventually I stopped. But I don't regret taking it. I took it for the same reason that I'd consider hormone therapy at some point: Because the side effects aren't permanent. And then the FDA took it off the market, because certain batches were contaminated with medications such as DES. [Editor's note: DES is a synthetic estrogen once given to women to help prevent miscarriage. The manufacturer of PC-SPES is out of business; the supplement is no longer available.]

So I've really collected information from multiple sources, and then I evaluate the source. So, for example, if I read about a Harvard study, I figure that's pretty reliable. But if someone is promoting something and I've never heard of it or them, I might look for information elsewhere and ask some people I respect before trying it.

*How often do you monitor your PSA levels? And what other evaluations do you undergo to make sure the cancer is not advancing?*

Since I was diagnosed, my PSA has moved up slowly from about 5.7 to about 12.2. So that's a little more than double in the last 10 years. If we knew that was the doubling rate then it'd be great—I'd live to 140—but of course the doubling rate could change.

I get my PSA tested every three or four months. I see my oncologist about once every nine or 10 months and occasionally have some tests to see if there's any indication of spread (see “Monitoring tests,” page 19). I've decided to avoid prostate biopsies for a couple of reasons. First of all, they hurt. Second of all, I believe the biopsies have risks. And third, there's no information that I would receive from a biopsy that would cause me to do anything differently.

It's not particularly nerve-racking to engage in active surveillance. I like to try to keep track of what's going on. One of the reasons I like PSA tests is that if my PSA goes up, it tends to reinforce the degree of persistence I have

in doing my program. Sometimes I am not as diligent as I should be. So I use the PSA as a kind of wake-up call (see “Does lifestyle matter?” below right).

*Your PSA levels have been elevated a few times, and you’ve found that these increases correlate with travel. Can you describe your experience with this?*

A few times, my PSA has spiked. One time, it went from 8.6 to 11.7. Another time, it went from 8.9 to 12.0. I suspect it has to do with changes in my lifestyle. On probably four occasions, when I traveled to India and then had a PSA test after my return, we found the PSA jumped. I think that’s because of a combination of stresses. First of all, just sitting in an airplane for 10 or 12 hours is hard on the body, not to mention traveling through all those time zones. And when I travel like that I tend to get off my regimen. I’ll eat vegetarian food, but it may not be exactly what I would eat at home. I tend to be less diligent with my supplements when I’m traveling. I don’t get massages or practice other stress-reduction techniques. But so far, once I’ve been home for a while, my PSA levels stabilize or come back down to where they were.

*What would have to change for you to consider being treated more traditionally? And what would you do?*

If my PSA started to shoot up significantly, or stayed elevated, then I would talk to my doctor about how I might use hormone treatments to keep the disease at bay. I consider hormone treatment something to keep in my “gunny-sack,” because although it involves side effects, for the most part they’re not permanent. Of course, before making a decision, I’d evaluate the known risks.

*Few people in 1996 decided on active surveillance. Knowing what you do now, would your treatment selection be the same?*

I know active surveillance isn’t for everyone. I just know that for me, this was the right choice. I’d make the same choice today that I did 10 years ago. But I’d be less afraid, and I’d be more decisive. You know, there’s more information now than there was 10 years ago. Now we know, for example, that prostate cancer metastases apparently may happen very early in the game, even earlier than the point at which I was diagnosed. And 10 years ago we didn’t know that my Gleason score [3+3] was only moderate risk. And then, of course, there’s been more information about alternative steps that help prostate cancer.

*Any other thoughts?*

This is sincere: I am glad to have cancer because it caused me to clean up my life. Today I feel better, I’m living healthier, and because of the lifestyle changes I’ve made, I’ve reduced my risk of heart attack, stroke, and other diseases. At least according to the actuarial tables, I’m going to live longer. So I’ve actually benefited from having this disease. ♥

### Monitoring tests

During a period of active surveillance, physicians may recommend the following tests to determine if prostate cancer is advancing:

- Endorectal MRI
- Abdominal-pelvic CT scan
- Bone scan

### Does lifestyle matter?

Research indicates that diet and other lifestyle changes can help lower PSA levels. See “The intensive lifestyle change study,” page 12.

## A patient's story:

### Why one man chose robotic-assisted laparoscopic prostatectomy

In the summer of 2005, Steve Henley was a successful 64-year-old financial services executive with a steady girlfriend. He was in great shape, often rowing for miles on the river. Receiving a diagnosis of prostate cancer came as a shock.

But Steve took his time before making a treatment decision. Diagnosed in September, he did not reach a decision until nearly five months later—and that was after shuttling between two major cities and consulting with a total of seven doctors and multiple friends. Two surgeons recommended open prostatectomy (done with an abdominal incision), two radiation oncologists recommended implantation of radioactive seeds, two medical oncologists advocated watchful waiting, and one surgeon suggested robotic-assisted laparoscopy—the option Steve ultimately chose.

*Could you describe in your own words the circumstances leading up to your diagnosis of prostate cancer?*

In July, I went in for my annual physical. I'd been rowing on the river for 15 miles and was pretty dehydrated. It was shortly after I finished my row that I went for my checkup. My internist did a digital rectal exam (DRE), and then I had a PSA.

The previous year, my PSA had been 3.5. But this time it came back at 6.0. The percentage jump alarmed my internist. So he suggested that rather than wait a couple of months to do another PSA test, that we do a follow-up test in two weeks. The second test came back at 4.4.

My internist sent all the information to the urology department. They thought the jump was significant and suggested that I have a biopsy.

About a month prior to the biopsy, I met with a nurse to go over the procedure. She told me, first of all, that I shouldn't have had a DRE before the PSA, and that second, all of that physical activity and dehydration would have affected my results. I also mentioned that I'd had sex in the two days before the PSA, and she said that before a PSA, you should abstain from sex for a couple of days, and that any one of those three things could have made the PSA jump the way it did. But regardless of that, they still felt I should have the biopsy.

So I had the biopsy in September. Of the 12 samples, 2 contained tissue that was 20% cancer.

At that point, I started seeing doctors for consultations. I had another PSA about a month later, during one of the consults, and that came back at 3.6.

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*Editor's note: To maintain his privacy, Steve's name has been changed. All other details are as reported.*

So the irony is, if I had somehow missed the earlier PSA tests, and just scheduled one in October, I never would have been diagnosed with cancer.

*And no one felt anything during a physical examination?*

No, and during all these follow-up visits, I certainly saw a lot of doctors. And they never felt any nodule or hardening during the DRE.

*Do you remember what you were told about the Gleason score, or other characteristics of the cancer after the biopsy?*

The Gleason was 3+3. Everyone that I talked with told me I had early-stage cancer and I had plenty of time to thoroughly investigate what I wanted to do.

*Can you share with us some of your emotions and thoughts when you got the diagnosis?*

They called me in and told me they'd discovered cancer. And I had a first meeting with one of the urologists, who explained all of the different ways to deal with the cancer. You know, I'm a Vietnam vet. I was a Marine helicopter pilot. And when I came back from Vietnam, I realized I'd developed an attitude where I don't worry about things. And that pervaded my reaction to cancer. I knew that I had to do my homework and decide what I wanted to do for myself, but it isn't something that put me into a tailspin.

*Who did you talk to, as you made your decision?*

I talked with a lot of people, in and out of the medical profession. I talked with surgeons who were leaders, as far as I could tell, in open surgery [*prostatectomy*], the leading seed-implant radiation oncologists, and then medical oncologists. But I also talked with men, like former fraternity brothers at college, who I knew had had prostate cancer, and started picking their brains. I also went online. The state where I live maintains a Web site listing doctors and the number of operations they've performed, and so I was able to determine who had done the most surgeries.

And you know, if you look at that list, it can scare the hell out of you. It made me realize that there are people who've had prostate surgery performed by a surgeon who does maybe one, two, or three of those operations a year. And you wonder, how could anybody make that decision? I know I wouldn't want someone who's done only one operation in a year to do me!

*What did the doctors advise?*

I first met with two doctors who did open surgery. Because my cancer was early stage, I never had the concern that maybe it was going to spread.

A bigger concern, to me, was retaining my potency. And neither one of the surgeons was able to give me any reassurance that they could preserve one of the neurovascular bundles, which would allow me to remain potent.


## Neurovascular bundles

These two portions of the prostate gland contain the nerves and blood vessels necessary for the maintenance of erectile functioning and potency.

## The Prostate Cancer Outcomes Study

This study involved 1,291 men ages 39–79 who filled out questionnaires asking about specific changes in urinary and sexual functioning following radical prostatectomy. When questioned 18 months or longer after treatment, 8.4% of men reported being incontinent, and 59.9% reported being impotent. These percentages indicate incontinence and impotence may be more common than other studies, which relied on patients volunteering specific information, have found.

SOURCE: Stanford JL, Feng Z, Hamilton AS, et al. Urinary and Sexual Function after Radical Prostatectomy for Clinically Localized Prostate Cancer: The Prostate Cancer Outcomes Study. *Journal of the American Medical Association* 2000;283:354–60. PMID: 10647798.

 See p. 48.

Both of them said, “Your cancer’s in the apex,” and they showed me how the nerve bundles came down right next to the apex. [See Figure 1, page 5.]

So they weren’t going to know until they got in there if they were going to be able to save the nerves. They were fairly confident they could save the other side. So that would give me at least a 33% chance that I could retain my potency.

*So the surgeons weren’t sure that they could save the neurovascular bundle, at least on one side.*

Right, and if they couldn’t save the neurovascular bundle on the one side, there would be only a 33% chance that I’d be able to have an erection after the operation. So I decided to seek some other opinions and look at other treatment options.

I met with two different radiation oncologists and two medical oncologists. And both of the medical oncologists thought I should consider active surveillance. For a while, I gave that serious thought. And I guess the bottom line was, I just wanted to have it taken care of. I didn’t want something hanging over me as time went on.

*Why were the oncologists recommending active surveillance? You’ve mentioned that the second oncologist you saw really made a strong argument for it.*

That’s right. First of all, he was concerned about what my quality of life would be like after surgery. I had shared with him my concern about retaining my potency.

*What kind of statistics did he provide?*

He said that some of the statistics out there are really bogus, that some of the doctors are not asking the hard questions. He cited the example of one well-known doctor, who asks his patients after surgery whether they were pleased with the surgery. And of course, if you think you don’t have cancer anymore, you’re going to say, “Sure, I’m pleased with my surgery.” But this doctor wouldn’t ask specific questions, like “Are you pleased with your potency?” or “Do you have any incontinence?” and so on. The doctor I was seeing had some problems with that, because he’d gone back to the same patients, and asked those questions, and came up with pretty grim results. So my doctor thought the chances of recovery after open surgery were a lot less optimistic than some of the statistics might suggest. [Editor’s note: Studies that use questionnaires to ask patients about specific problems tend to find a higher incidence of particular side effects than other sampling methods. See, for example, “The Prostate Cancer Outcomes Study,” at left.]

*And what did the radiation oncologists advise?*

I was really impressed with both men. They talked about the implantation

of radioactive seeds (brachytherapy). I said to one of them, “You know, I’m getting all this information and I’m in overload here. So if you were in my position, what would you do?”

And he said, “Well, I’m 20 years younger than you. So if I had prostate cancer, I would have surgery. Because I’m most concerned about living a long life.”

And I said to myself, “Look, pal, I want to live a long life too!”

*Did he provide evidence that surgery would make an individual patient live longer?*

No, he didn’t. The issue is that they don’t have enough statistics on the seed implants to know whether they are knocking cancer totally out of the system. But what persuaded me was that here was this seed doctor saying, “If it were me, I’d have surgery.” That immediately eliminated seeds for me.

*Did either of the radiation oncologists mention external beam radiation?*

Both of them said that was something that could be used, but they focused on their own area of expertise, which was brachytherapy.

*So then what happened?*

Well by this point it was December, and I was less than happy with the information I was getting. I knew I wasn’t going to have brachytherapy. So I made an appointment for surgery in March. Because even though doctors were telling me I had a long time to think about all the options, I was really feeling like it was time to make a decision, because I’d been looking at options for three months.

In the meantime, two of my fraternity brothers were diagnosed with prostate cancer. One had open surgery in another city. I talked with him and his wife by phone, on speakerphone so that I could talk to both of them. And they were very candid with me about their life and his recovery from cancer surgery. He’d had surgery in mid-July, and I talked with them in early October. He told me that by then his incontinence was under control, but even though he was taking Viagra on a daily basis, he still wasn’t getting any sign of an erection. And it had been three months. [*Editor’s note: See the next issue of Perspectives for a look at an investigational protocol using Viagra.*]

*Have you talked with him since then? Has there been any improvement?*

I did talk to him right before I had surgery. By then it had been eight months, and he still wasn’t able to have an erection.

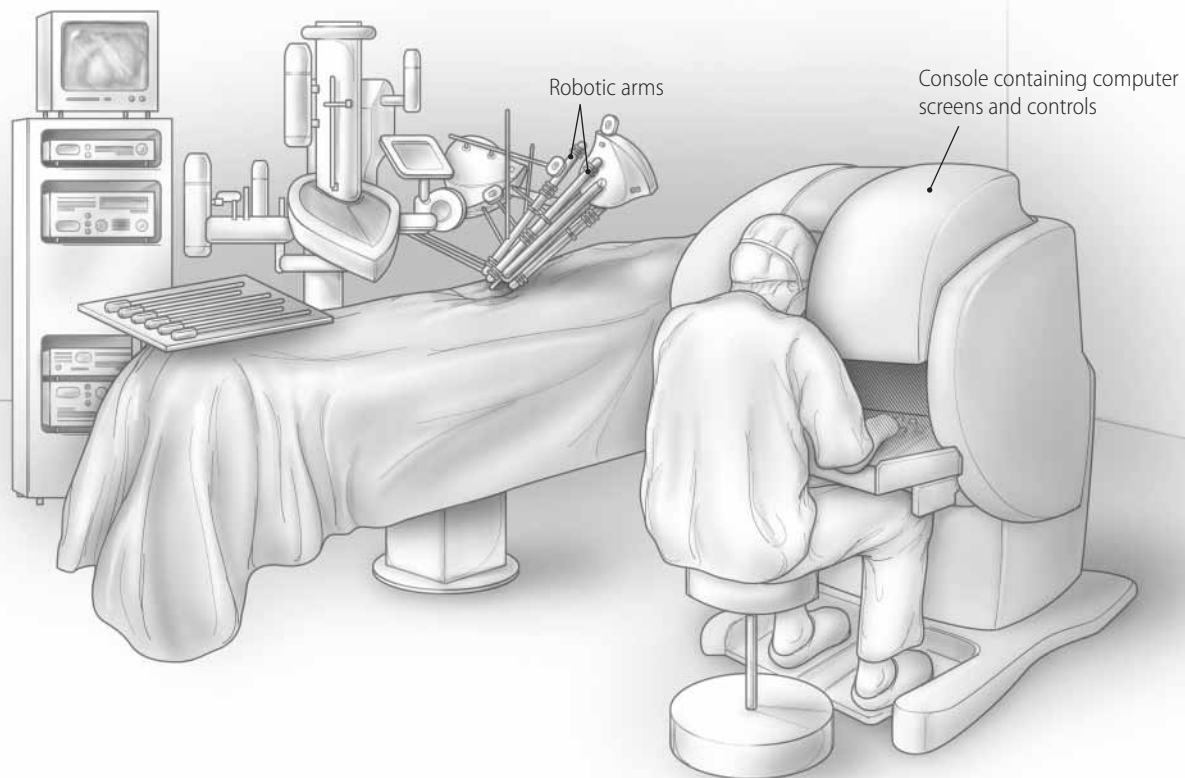
My other fraternity brother found out that he had prostate cancer a week after I did. And we were sort of holding hands and exchanging notes while we tried to make a decision. He’d read a book by a well-known surgeon, and

decided to make an appointment with him to discuss open surgery. But this book also mentioned another doctor, in the same hospital, who did laparoscopic surgery. The meeting with the first surgeon went well. But as my fraternity brother and his wife were leaving the hospital, he said, “I’m just going to call this guy who does laparoscopy and ask if he can see me.” Fortunately the second doctor was there and actually had time to see him.

Eventually, my friend decided to have laparoscopic surgery. He had the surgery in January. His recovery time was really quick. So he urged me to consider it. And I did.

But my girlfriend had been after me ever since I was diagnosed to look at robotic surgery because her investment advisor had recommended that

**Figure 4. Operating by remote control**



To perform a robotic-assisted laparoscopic prostatectomy, the surgeon sits at a console several feet away from the operating table and manipulates robotic arms, which are fitted with tiny cameras and surgical instruments, to locate and remove the diseased prostate gland. The console contains two full-color computer screens that provide a magnified, three-dimensional view of the prostate and surrounding tissues. The surgeon guides the robotic arms by manipulating manual controls while watching the screens.

Proponents of this approach claim that robotic-assisted laparoscopic prostatectomy offers greater magnification and surgical precision than the alternatives, but thus far the evidence indicates that success rates and chances of complications are about the same as for traditional laparoscopic prostatectomy and radical prostatectomy (so-called “open” surgery).

she invest some money in the company that makes one of the robotic devices. At first I said, “Yeah, okay.” But I didn’t take it seriously.

One of her friends knew that I had cancer and called her up to say, “Did you or Steve see the article on robotic surgery?” The article had just run in a magazine. We hadn’t seen it, so we looked it up, and the article included an interview with a patient who had undergone robotic surgery. He talked about how easy it was, and how quickly he recovered, and was able to do all of the activities he wanted to do.

The article mentioned two doctors in another city. So I thought, “As part of my investigative research, I’ve got to go talk with both of these guys.” So I made an appointment to see them in February. My girlfriend went with me. But I was so impressed with the first surgeon that I canceled the meeting with the second.

*What is it that impressed you?*

Well, first of all, his background. He was originally trained as a surgeon who did open prostatectomies. But then he became intrigued with laparoscopic surgery, so he went to France to learn the technique, and then started using it in his own practice. When robotic laparoscopic surgery came out, he also took the time to learn it [see Figure 4]. So I saw someone who was on the cutting edge, who had taken the time to ensure he could be the best surgeon he could be. It just gave me a lot of confidence.

One of the questions I asked him about the surgery was, “I’ll accept that you’re confident about running the robot. But what if the robot breaks down halfway through the surgery?”

He said, “I’ll open you up and finish.”

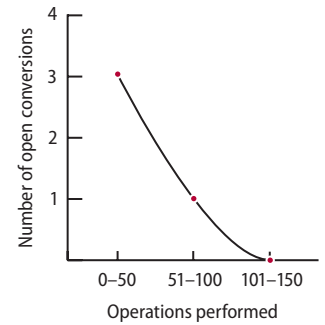
*That’s an important consideration, because many people who are trained to do laparoscopic surgery haven’t been trained to do open surgery. Yet sometimes they have to switch gears in the middle of the operation and perform an open prostatectomy [see Figure 5].*

That’s exactly what he said. But even more important, in my mind, was his answer to another question. I said to him, “You’ve been trained in all three disciplines, so why do you think robotic surgery is the best choice for me?”

And he said, “The clarity of vision, the magnification, offered by robotic surgery is about 12 times greater than using your eyesight during open surgery. So when I’m putting a stitch in, it’s so clear, it improves the precision.”

He even said that with this technique, he can see the color differentiation, where the cancer begins and ends. And he said you just can’t do that during open surgery. The other thing he mentioned is that there’s virtually no blood loss. And the recovery time is significantly better.

**Figure 5. Practice makes perfect**



The likelihood that a surgeon performing laparoscopic prostatectomy will have to switch to open abdominal surgery in order to complete the operation goes down significantly with practice, measured in the number of operations performed.

SOURCE: *Journal of Urology*, July 2005.

*Did he mention anything about the visualization of the neurovascular bundles?*

Yes, he felt pretty confident that with the increased magnification, he would be able to move them aside, and remove the prostate with no problem. He said, “If the cancer has spread into the seminal vesicles, then obviously we have to deal with that. And we won’t know until the operation.” But he seemed pretty confident that after the operation I’d be in good shape.

*Did you consider having robotic surgery closer to home?*

You know, I did look into it. But I did some research, and it looked like there weren’t many people doing this at the time in the city where I live, and they didn’t have a lot of experience. One surgeon had done 50 of these operations. The doctor I met with had done about 400. So I’m thinking, “Okay, 50 versus 400. I think I’ll go with the guy who’s done 400.”

*What kind of logistics were necessary, with you being in one city and the operation being done in another?*

There were some logistical challenges. I ended up doing the preoperative testing at a hospital near my home, and then had it sent to the surgeon in the other city. He was willing to accept their medical tests.

During the operation, they inserted a catheter, which is normal. And he was also comfortable with me having the catheter removed near my home, but the hospital up here didn’t want to get involved, because it wasn’t their operation. So I ended up traveling to the other city to have the catheter removed.

*How long did you have it in place?*

Five days.

*And tell us a little more about the operation, and how you felt afterward.*

My girlfriend and I stayed in the hospital the night before. They actually have some rooms you can rent. I thought I was being operated on at 10 a.m., and I had to be in the prep room at 8 a.m. But there was a miscommunication, and I didn’t get into the operating room until the afternoon. So I spent all day in the waiting room, which was annoying. But they operated on me at 4:30 p.m. They were finished by 6 p.m. I spent the night in the hospital, and at 10:30 the next morning, I walked out of the hospital.

*How did you feel?*

I felt great. We took a cab to the train station. We took the train home. We then caught a cab to my condo. I walked up four flights of stairs as briskly as I’d ever walked up the stairs. And I felt terrific.

*Any postoperative complications?*

No.

*And what did the final pathology show?*

They felt they had a clean margin, that they got all the cancer out.

*Did they sample the lymph nodes?*

They did, and the lymph nodes were clean. No cancer.

*So if you had to offer advice to readers of Perspectives, who may be trying to weigh all the options, what would you tell them?*

I think it's important that you reach a decision that you're comfortable with, and it took me a long time to get to that point where I was comfortable.

By the time I got into the operation, I'd reached the point where I thought, "Okay, whatever happens, happens." I believe I made the right choice for me. And I can live with whatever happens. And I think everybody needs to get to that point.

Of course, I had the luxury of time. I didn't have the pressure of an aggressive cancer. So I felt confident that my cancer would be cured. My larger concern was my potency.

*How has your recovery gone?*

My potency returned a month after the operation. The incontinence has been a problem. I talked with my doctor a few weeks ago, and he suggested a biofeedback session at a hospital near my home. He said that I may not be doing the Kegel exercises correctly. But he said, "I promise you that your incontinence will be resolved. You've just got to be a little patient." [Editor's note: A Kegel exercise is an exercise for the pelvic floor muscles that is used to prevent and treat incontinence.]

*What was the biofeedback session like?*

I've only had one. And I have another session in a couple of weeks. Basically they put a sensor on my stomach, and one in my anus. And they hook the sensors up to a computer. I then did a Kegel exercise. And the graph showed that I wasn't using my abdominal muscles, so I was doing the exercises correctly. But my sphincter muscle isn't strong enough to hold the contractions. So the nurse gave me a set of exercises about how to do the Kegels better.

*Has the incontinence been getting better?*

For several months now, I don't need a pad anymore to get through the night. You know, it's interesting because I row, and I don't have a problem. If I'm sitting at my desk, I don't have a problem. My biggest problem is if I'm lying on a couch, watching television. And recently I went to an outdoor production of one of Shakespeare's plays, held in a public park. I was sitting on a blanket. And I was a mess. So it has something to do with the position I'm in.

*I know you're happy with your potency. Did you do anything in particular to speed your recovery?*

The surgeon had advised me that the more sexual activity that someone has had leading up to surgery, the better their chances of recovery on the other side. If someone is sexually inactive, that makes it more difficult. I'd heard that from other doctors as well.

*Yes, that's true. We tell that to patients all the time.*

[*Laughing*] So before the operation, I probably focused more on having sexual activity than doing my Kegel exercises.

*Have you had a postoperative PSA?*

I did. It was less than 0.1. And the digital exam showed nothing.

*So knowing what you do now, would you still make the same treatment choice?*

Without question. I'm glad this is behind me.

*Any parting thoughts?*

There's a lot of information out there. And it's easy to get overloaded. The more information I got, the less comfortable I felt with my decision—until I found robotic surgery.

It's not an easy decision for anyone to make. But, I think, the more people you talk with and the more familiar you can get with the issues, the easier it is to make a decision that's right for you. It's a mistake to decide on one course of action without knowing what the alternatives are. ♥

# Your benign prostatic hyperplasia medication: When to consider a change

## A look at treatment options and trade-offs

If you are like many of the 14 million men in the United States who have been diagnosed with benign prostatic hyperplasia (BPH), you've probably been taking the same medication, at the same dose, for years. If so, consider the experiences of two patients, both of whom were taking some type of medication for BPH. Their names have been changed, but all other details are accurate (see "Jack Muriel" and "Henry Banks," at right).

Jack and Henry experienced unexpected consequences while taking a BPH medication. Fortunately none of these consequences had long-lasting health effects—and they could be avoided in the future by making some adjustments. In Jack's case, the problem was mixing a BPH medication with one for erectile dysfunction. Although many men use both medications without difficulty, some may need to take precautions. Henry might have been able to avoid a visit to the emergency room if, before getting a computed tomography (CT) scan, he'd told the radiologist that he had been taking a medication for severe BPH.

Certainly some type of adverse event, such as these men experienced, might make you wonder if it's time to adjust the dose of your medication or perhaps even change medications. But there are other considerations as well. Every man is different. In the pages that follow, you'll learn about the types of issues many men with BPH have confronted, and what situations might indicate it's time to consider a change in medication. (A concise summary of how these medications work, side effects, and treatment considerations is provided in Table 5, page 41.)

### Issues to consider

The two classes of drugs currently approved to treat BPH—alpha-1 blockers and 5-alpha-reductase inhibitors—work in entirely different ways, and therefore raise different types of issues. So it's important to understand these differences as you evaluate which medications might be right for you.

Simply put, alpha-1 blockers deal with the "going" problem by relaxing certain muscles in the prostate and urinary tract, while 5-alpha-reductase inhibitors deal with the "growing" problem by reducing the size of the prostate (see Figure 6).

The alpha-1 blockers are classed into two groups. The selective agents, alfuzosin (Uroxatral) and tamsulosin (Flomax), work primarily on the tissues of the urinary tract. The nonselective agents, doxazosin (Cardura) and terazo-

### Jack Muriel

At 64, Jack was taking tamsulosin (Flomax) for moderate BPH but otherwise was in good health. Recently retired, he looked forward to a weekly round of golf with friends at a local country club. One evening, while driving home to meet his wife for dinner, Jack suddenly became lightheaded. He felt as if he were about to faint. He managed to pull the car over to the side of the road and call for help. While dialing, he thought, "Maybe I shouldn't have taken the Viagra and Flomax at the same time."

### Henry Banks

At 77, Henry was generally in good health, but had been taking terazosin (Hytrin) for his BPH for years. At one point, after Henry experienced a bout of unexplained abdominal pain, his internist ordered an abdominal CT scan to determine the problem. As instructed by the radiology department, Henry drank large quantities of water before the procedure. The CT scan itself went fine, but afterward, Henry found he could not urinate, even though his bladder was full. Instead of returning home after the CT scan, Henry wound up in the emergency room, where he had to have a catheter inserted.

sin (Hytrin), affect both the urinary tract and other tissues elsewhere in the body. The 5-alpha-reductase inhibitors, which include dutasteride (Avodart) and finasteride (Proscar), act directly on the prostate.

Other medications are in development (see “Anticholinergic drugs,” page 33, and “PDE-5 inhibitors,” page 35), but are not yet available. So for now, you’ll have to weigh the relative risks and benefits of alpha-1 blockers and 5-alpha-reductase inhibitors.

When it comes to recommending one drug or another, urologists often use some general guidelines: Alpha-1 blockers are better at relieving urinary symptoms such as difficult or frequent urination, and are best for men with smaller prostate glands. But 5-alpha-reductase inhibitors may be in order if you have a large prostate gland or have not obtained sufficient relief from alpha-1 blockers. And they have a stronger track record for reducing the chance that you’ll need surgery or will experience complications such as acute urinary retention. Sometimes the medications are prescribed in combination.

### Speed of relief

The alpha-1 blockers work quickly, taking effect in days to weeks. But the nonselective agents may require some patience, as doses have to be increased slowly at first, to avoid lowering your blood pressure too much (see “High blood pressure,” page 32). Doctors usually start with 1 milligram (mg) at bedtime, then gradually increase it as needed to a maximum of 10 mg of terazosin or 8 mg of doxazosin. This process, known as titration, may be frustrating for you as well because you will need to wait to find the correct therapeutic dose.

Dosing is simpler for the selective alpha-1 blockers. For tamsulosin, you take 0.4 mg or 0.8 mg half an hour after dinner. Alfuzosin is a time-release formulation, so a single 10-mg tablet is taken once a day immediately after a meal.

With the 5-alpha-reductase inhibitors, it takes longer to feel the results. These drugs shrink the prostate by reducing levels of the male hormone dihydrotestosterone (DHT), which promotes prostate growth. Levels of DHT fall precipitously after several weeks of taking a 5-alpha-reductase inhibitor, but it may take at least three to six months, and perhaps even longer, before you notice any improvement in urine flow.

### Combination therapy

When it comes to BPH, are two drugs better than one? The Medical Therapy of Prostatic Symptoms (MTOPS) study indicated that the answer may be yes—at least for some men. In the study, 3,047 men with BPH were randomly assigned to take doxazosin (Cardura), finasteride (Proscar), a combination of the two, or a placebo. After roughly four and a half years of observation, the combination reduced the risk of BPH progression (symp-

### Time to change?

Any of the following suggests that you should re-evaluate your BPH medication:

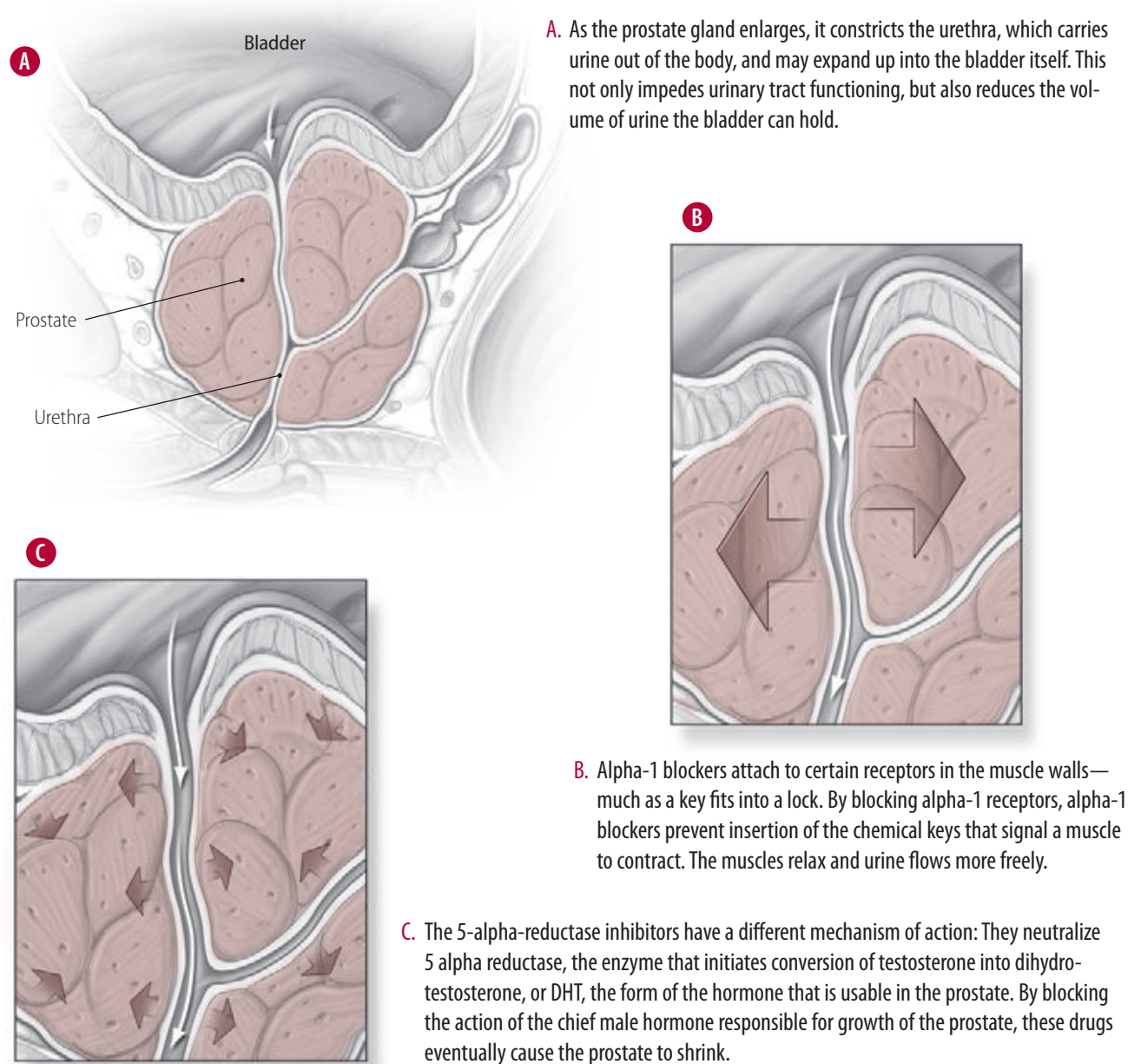
- Your BPH symptoms worsen, even though you are taking your current medication.
- You notice side effects that weren’t affecting you before.
- You start taking a drug for some other medical condition—or add drugs to an existing regimen (for example, you add another medication to help control your high blood pressure).
- You start taking a drug for erectile dysfunction.

toms getting worse) by 66% when compared with placebo, significantly more than either drug alone. Compared with placebo, doxazosin reduced BPH progression by 39%, and finasteride reduced it by 34%.

A 2006 reanalysis of the MTOPS data according to prostate gland size found that combination therapy provided the most benefit to men whose prostate glands were 25 grams or greater in size (see “MTOPS study and reanalysis,” page 32).

Some men with large prostates try combination therapy to get fast relief

**Figure 6. How BPH medications work**



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### MTOPS study and reanalysis

McConnell JD, Roehrborn CG, Bautista OM, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. *New England Journal of Medicine* 2003;349:2387–98. PMID: 14681504.

Marberger M. The MTOPS Study: New Findings, New Insights, and Clinical Implications for the Management of BPH. *European Urology Supplements* 2006;5:628–33. PMID: In process.

 See p. 48.

for their symptoms from the alpha-1 blockers (see “Speed of relief,” page 30). In six months or so, when the 5-alpha-reductase inhibitors begin taking effect, these men may stop taking the alpha-1 blockers.

However, you should consider two additional pieces of information when contemplating whether to start combination therapy: cost and side effects. First, taking two pills is more expensive. If you have to pay for medications on your own, or if your insurance company requires some type of co-pay, you may want to figure cost into the equation (see “Cost,” below). Second, although the MTOPS study found that side effects were similar whether men took one drug or the combination, our panel of Harvard experts felt differently, based on the patients they see (see “Combination medical therapy,” page 47).

### High blood pressure

The nonselective alpha-1 blockers block alpha receptors in the heart and blood vessels as well as in the prostate, lowering blood pressure in the process. While these agents are usually not the first choice for blood pressure control, they may be a good choice for men who have both BPH and high blood pressure. If you want to limit the number of different medications you are taking, ask your doctor whether using a nonselective alpha-1 blocker might enable you to control both your BPH and your blood pressure—and then monitor both your urinary symptoms and your blood pressure to make sure the medicine is really working for you.

If you are already on another medication to control your blood pressure, or are taking an erectile dysfunction drug, then taking a nonselective alpha-1 blocker carries the risk that you will experience lightheadedness, faintness, dizziness, or postural hypotension (a drop in blood pressure that occurs when you sit or stand quickly, as when getting up from a chair or out of bed). Although a panel of Harvard experts thought the risk of hypotension was minimal (see “Using BPH and erectile dysfunction drugs,” page 42), it’s still worth knowing about. Sudden episodes of low blood pressure can be dangerous if you already have some type of vascular disease, because it increases your risk of suffering a heart attack or stroke.

Similarly, because of these side effects, the nonselective alpha-1 blockers may not be the best choice for you if your blood pressure is already on the low side.

The selective alpha-1 blockers, alfuzosin and tamsulosin, have less of an impact on blood pressure, so they may be good alternatives in these situations. (Of the two, tamsulosin seems to affect blood pressure levels the least.) Or consider taking a 5-alpha-reductase inhibitor.

### Cost

The nonselective alpha-1 blockers (doxazosin and terazosin) are available

now in generic as well as brand name formulations, and so may save you some money (see Table 4). Of course this may also depend on what type of drug coverage is included in your health insurance plan, and how much of a co-pay you need to contribute.

**Sexual side effects**

Because they affect levels of the male hormone testosterone, the 5-alpha-reductase inhibitors may cause a variety of sexual side effects. In the original clinical trials, 3.7% of men taking these drugs (and 4%–6% by some other estimates) developed erectile dysfunction. Another 3.3% of men experienced a decline in libido, while 2.8% had problems ejaculating during an orgasm.

In addition, one of the selective alpha-1 blockers, tamsulosin, causes ejaculation problems in some men who take it. The other alpha-1 blockers may cause less of this problem.

Erectile dysfunction is treatable with three medications, and it is generally safe to take these drugs when you are taking your BPH medication, whether it is an alpha-1 blocker or a 5-alpha-reductase inhibitor; however, we offer some important cautionary advice (see “Medications for erectile dysfunction,” page 34, and “Using BPH and erectile dysfunction drugs,” page 42).

If you develop problems with ejaculation during sex, the solution depends on what medication you are taking. If you are taking a 5-alpha-reductase inhibitor, the only way to resolve the ejaculation difficulties is to stop taking the BPH medication, so you may need to decide on another medication (or surgery) to deal with your urinary difficulties. However, if you are taking tamsulosin, you may be able to alleviate ejaculation problems by taking the drug every other day (see “Alternate days,” page 34).

**Anticholinergic drugs**

These medications are used to quiet overactive bladder muscles, which can lead to urinary incontinence. Investigators have discovered in the past few years that more than half of men with BPH also suffer from overactive bladder, and that this may further exacerbate urinary difficulties. Researchers are now investigating whether taking anticholinergic drugs can ease BPH symptoms.

**Table 4. Cost of BPH drugs compared**

The costs below are based on average wholesale prices to pharmacists and the lowest dosage; costs to patients may be more.

Drug class	Generic name (brand name)	Estimated cost per month for generic, if available	Estimated cost per month for brand name medication
Nonselective alpha-1 blockers	doxazosin (Cardura)	\$18–\$29	\$40
	terazosin (Hytrin)	\$18–\$48	\$68
Selective alpha-1 blockers	alfuzosin (Uroxatral)	n/a	\$71
	tamsulosin (Flomax)	n/a	\$71
5-alpha-reductase inhibitors	dutasteride (Avodart)	n/a	\$92
	finasteride (Proscar)	n/a	\$100

SOURCE: 2006 Red Book (Montvale, NJ: Thomson PDR, 2006).

Gynecomastia (breast enlargement), another possible side effect of the 5-alpha-reductase inhibitors, is rare but is distressing when it occurs. Stopping the medication may reverse the problem. But not always: Some men have had to undergo breast reduction surgery—or learn to live with the changes.

### Alternate days

Investigators asked 140 men with BPH to take 0.4 mg of tamsulosin (Flomax) daily for three months. If the men responded to tamsulosin, they were randomized to one of three groups. One group continued taking the medication daily, the second took the same dose every other day, and the third stopped taking the drug. Men taking tamsulosin every other day did just as well as those taking it daily, and experienced fewer side effects such as ejaculation problems.

SOURCE: Yanardag H, Goktas S, Kibar Y, et al. Intermittent Tamsulosin Therapy in Men with Lower Urinary Tract Symptoms. *Journal of Urology* 2005;173:155–7. PMID: 15592062.

 See p. 48.

### Medications for erectile dysfunction

Three medications have been approved for the treatment of erectile dysfunction: sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra). These medications are all PDE-5 inhibitors, which generate nitric oxide, a chemical that enables arteries to widen. The increased blood flow to the penis helps to produce an erection. The problem is that arteries elsewhere in the body widen as well, causing a slight drop in blood pressure.

If you are considering an erectile dysfunction medication, you don't have to worry if you are also on one of the 5-alpha-reductase inhibitors for your BPH: The drugs can be taken together without adverse effects. However, if you are currently using, or considering, an alpha-1 blocker, you may want to take some precautions when adding one of the PDE-5 inhibitors.

Here's why: Because the PDE-5 inhibitors cause a system-wide drop in blood pressure, theoretically they can exacerbate the blood pressure-lowering action of the nonselective alpha-1 blockers doxazosin and terazosin. This seems especially to be a problem when taking sildenafil (Viagra) and vardenafil (Levitra); tadalafil (Cialis) is a longer-acting PDE-5 inhibitor, and the risks are less clear.

As a result, some doctors recommend that if you are using a nonselective alpha-1 blocker for BPH, you should avoid taking an erectile dysfunction medication altogether. However, our panel of Harvard experts think the concerns are overblown (see "Using BPH and erectile dysfunction drugs," page 42). If you don't want to stop using a nonselective alpha-1 blocker for your BPH, you can make sure you take the PDE-5 inhibitor at different times of the day (take one medication after lunch, say, and the other in the evening) to avoid problems.

Or you can lower the dose of your alpha-1 blocker or PDE-5 inhibitor. That is what Jack Muriel eventually decided to do. He'd taken his BPH medication, Flomax, along with Viagra before heading home to have dinner with his wife. The combination created the dizziness that caused him nearly to run off the road. His doctor suggested he try lowering his dose of Viagra in the future, to 25 mg (from the 100–200 mg he'd been taking), because that would lessen the chance of dizziness if he took it along with the Flomax. Or, if that dose was not sufficient, he could try 50 mg of Viagra. But to prevent problems, he needed to make sure that he took it at least four hours before (or after) he took the Flomax.

## Prostate cancer

The Prostate Cancer Prevention Trial (see “For more information,” page 6) showed that taking one of the 5-alpha-reductase inhibitors, finasteride, reduced the risk of developing prostate cancer by 24.8%—an astounding amount, and a result that would normally change the practice of medicine.

But here’s the bad news—and why you need to consider your choice of finasteride carefully: Men in the study who took finasteride were more likely to develop high-grade cancer (the type more likely to spread and become life-threatening) than those taking a placebo. In the PCPT study, high-grade prostate cancers developed in 37% of the men taking finasteride who developed tumors (6.4% of all the men taking finasteride), compared with 22% of the men taking placebo who developed tumors (5.1% of all men taking placebo).

So what’s going on? It’s not clear. The PCPT study has generated heated discussion, and one leading theory is that because finasteride shrank the prostate gland, doctors had a smaller target to sample, and were therefore more likely to find cancer. It is unclear whether the findings also apply to dutasteride, but because the drug is in the same class, most researchers think it does. For now, check with your own urologist for advice about what you should do. Future issues of *Perspectives* will revisit this important topic.

**Pay attention to PSA levels.** If you decide to take a 5-alpha-reductase inhibitor, whether it’s only for your BPH symptoms or because you also want to reduce your overall risk of prostate cancer, you’ll need to understand how these medications will affect your PSA levels. In general, 5-alpha-reductase inhibitors tend to reduce PSA levels by about 50%, although the actual reduction varies from man to man. It is important to obtain a baseline PSA value before beginning treatment with one of these medications, and then have another after 6–12 months, to see how much the PSA has gone down after treatment. This follow-up PSA then becomes your new baseline.

You’ll need to figure this new baseline into your calculations as you monitor your PSA in the future. So, for example, if you start taking a 5-alpha-reductase inhibitor, and your PSA falls from 3 to 1.5, that’s to be expected. But if it should double over the course of a year, say from 1.5 back to 3, talk with your doctor about whether to have a prostate biopsy (a topic covered in a future issue of *Perspectives*). Even though a value of 3 is considered “normal” in men not taking a 5-alpha-reductase inhibitor, a PSA value that doubles within a year of beginning one of these medications could indicate that cancer is present.

## Acute urinary retention

Henry Banks developed acute urinary retention after drinking large quantities of water for a CT scan. This is a medical emergency, because if someone is unable to urinate and excrete urine, over time pressure that builds up

## PDE-5 inhibitors

Could these medications, already approved to treat erectile dysfunction, also alleviate BPH symptoms? The answer may be yes, according to early studies of sildenafil (Viagra) and tadalafil (Cialis)—although the dosing is different than for erectile dysfunction. The medications may help by relaxing smooth muscle within the prostate, thereby improving the flow of urine. However, more research is needed.

## BPH progression

Although BPH symptoms often remain stable, one study found that progression was likely in men with the following clinical profile:

- Age 62 years or older
- Prostate size of 31 grams or greater
- PSA of 1.6 ng/ml or greater
- Urine flow less than 10.6 ml per second
- Post-void residual of 39 ml or greater


SOURCE: Crawford ED, Wilson SS, McConnell JD, et al. Baseline Factors as Predictors of Clinical Progression of Benign Prostatic Hyperplasia in Men Treated with Placebo. *Journal of Urology* 2006;175:1422–7. PMID: 16516013

 See p. 48.

## Two additional benefits

A clinical trial involving more than 3,000 men, comparing finasteride (Proscar) with placebo, found that only 3% of men taking finasteride developed acute urinary retention (versus 7% taking placebo), and 5% eventually required surgery (versus 10% taking placebo).

SOURCE: McConnell JD, Bruskewitz R, Walsh P, et al. The Effect of Finasteride on the Risk of Acute Urinary Retention and the Need for Surgical Treatment Among Men with Benign Prostatic Hyperplasia. *New England Journal of Medicine* 1998;338:557–63. PMID: 9475762.

 See p. 48.

in the bladder can adversely affect the kidneys, possibly leading to kidney failure—which is life-threatening.

For most men, of course, the most tangible worry about acute urinary retention is that they may have to have a catheter inserted to relieve pressure on their bladder—which is simply uncomfortable, bothersome, and potentially embarrassing (the catheter can sometimes leak, causing accidents). Sometimes a man can be weaned from the catheter and return to taking a BPH medication, but not always. A man who has developed acute urinary retention may need to consider surgical options to alleviate his symptoms.

To reduce your risk of developing acute urinary retention, you have two options. The first is to take some common-sense precautions, no matter what BPH medication you are on. Watch your intake of fluids, especially if you will be unable to urinate for a while (such as when you're at a sporting event or on a long airplane trip). If your doctor recommends a medical test that requires you to drink fluids ahead of time, as Henry did, mention that you are taking a BPH medication and ask what your doctor advises.

Second, if you are at risk for acute urinary retention, it means your symptoms have progressed so that your urinary difficulties are moderate to severe in intensity (see “BPH progression,” above left). It may be time to consider switching to a 5-alpha-reductase inhibitor. Because these medications reduce the size of the prostate and thus ease constriction of the urethra, they also reduce the risk of developing acute urinary retention and having to undergo surgery (see “Two additional benefits,” at left).

## Making a decision

Obviously the decision about whether to make some change in your medication regimen for BPH—whether it involves changing the dose or switching medications—is a complex one. You alone know how bad your urinary symptoms are, and what other health issues and trade-offs you need to consider.

Table 5, page 41, summarizes the salient information by drug and suggests the type of men who might want to consider taking one drug rather than another. Ultimately, of course, you are the authority when it comes to your own body, and different people metabolize drugs in different ways, so these general guidelines should be viewed as just that—general.

Even so, the information in this table, and in the rest of this article, may help you clearly evaluate your medication options. And if you ultimately decide that medications are not providing you with sufficient relief, it may be time to look into surgical options (to be covered in upcoming issues of *Perspectives*). ♥

# Harvard experts discuss benign prostatic hyperplasia drug treatments (Part 1 of 2)

## A frank discussion of risks and benefits

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Benign prostatic hyperplasia (BPH) is one of the most common disorders affecting men as they grow older. Yet there is much confusion about the best way to treat this disorder, in part because men taking medications for BPH are also likely to be taking other drugs for common medical problems, which may lead to adverse interactions and exacerbated side effects.

*Perspectives on Prostate Disease* invited three Harvard experts to participate in a roundtable discussion to share their thoughts about the relative benefits and risks of current BPH medications. The next issue of *Perspectives* will present their thoughts about the best surgical approaches to BPH. Participants included:

- **Dr. Kevin Loughlin**, professor of surgery (urology) at Harvard Medical School, who is senior surgeon and director of urologic research at Brigham and Women's Hospital and staff urologist at Harvard University Health Services, a large university health program that serves the needs of Harvard students, faculty, employees, and their families.
- **Dr. Abraham Morgentaler**, associate clinical professor of surgery (urology) at Harvard Medical School and director of Men's Health Boston. Dr. Morgentaler specializes in diseases of the prostate and has a particular interest in treating erectile dysfunction, low testosterone levels, and BPH. He has published widely on the issue of erectile dysfunction.
- **Dr. Martin Sanda**, associate professor of surgery (urology) at Harvard Medical School and director of the Prostate Care Center at Beth Israel Deaconess Hospital. Dr. Sanda has extensive experience in prostate cancer and BPH and has devoted much of his professional research to evaluating prostate-related treatment outcomes and developing new therapies.
- **Dr. Marc B. Garnick**, editor in chief of *Perspectives*, moderated the discussion.

In the following pages, you'll learn what they think about who needs to be treated, what medications should be prescribed, and what side effects you need to be aware of. In short, after reading this article, you'll become a more discerning critic of the statements made during BPH drug advertisements that air during televised sporting events—and much more able to work with your doctor to make your own treatment decisions.

**In brief:** One of the most vexing issues for people with BPH is deciding whether to begin treatment for urinary difficulties and other symptoms. Studies of the natural history of BPH over a period of up to five years show that, even without treatment, symptoms will not worsen in 16% of men, and they will actually improve in 38% of men.

### Who needs to be treated

**POPD:** *What criteria do you use in determining whether to recommend treatment?*

**MORGENTALER:** One of the issues we're always struggling with is who really needs to be treated at all. Some men may have relatively mild symptoms, in the spectrum of what we see, but they really are bothered by them and want to be treated, while other men may have really bad symptoms and are not interested in treatment at all. BPH treatment really comes down to patient preference and the impact of the condition on a person's life.

**SANDA:** I agree. When we talk about treatment, we're really talking about symptom management and symptom relief. The only time we'd urge someone without symptoms to begin medical treatment for BPH is if he began to suffer adverse consequences, such as infection due to retained urine or acute urinary retention, or if tests reveal scarring of the bladder, or any other sign that some type of irreversible damage is occurring in the bladder or kidneys. In such situations, we'd recommend treatment even if the patient is not particularly bothered by symptoms.

**LOUGHLIN:** There's actually a fairly narrow spectrum of absolute indications to treat BPH. Most people, probably more than 90%, are coming for relief of symptoms.

### What medications should be prescribed

**In brief:** Two classes of medication are available to treat BPH: alpha-1 blockers and 5-alpha-reductase inhibitors. It is not always apparent which medication is best for which patient.

**POPD:** *What criteria do you use in determining the type of BPH medication to recommend?*

**LOUGHLIN:** In general, alpha-1 blockers are best used in men with smaller prostates, 35 grams and smaller, and 5-alpha-reductase inhibitors are better for men with larger prostates, 55 grams and larger. This approach has been endorsed by several respected studies. Now, it's not absolute. There's judgment involved on the part of the urologist and the patient, but I think it's a useful way to think of it, that with smaller glands you tend to use alpha-1 blockers, and with larger glands you tend to use 5-alpha-reductase inhibitors.

**POPD:** *How is the size of the prostate best determined?*

**LOUGHLIN:** Your doctor can provide you with a rough estimate by doing a digital rectal exam. The other way to find out is to undergo a transrectal ultrasound—although that is usually ordered only if prostate cancer is suspected.

Of course, prostate size isn't the only issue. Something else to consider is that alpha-1 blockers have a very rapid onset of action, days to weeks. 5-alpha-reductase inhibitors have a slow onset of action, three to six months.

So in addition to size of the prostate gland, you need to understand from the patient how bothered he is by his symptoms and how long he can wait for relief.

**MORGENTALER:** Definitely one factor that drives the choice of medication is how quickly a patient wants to see results. It's very difficult to take a medication day after day, when it may not really have much impact for a few months. I think part of what drives the choice of alpha-1 blockers is that a patient will get relief fairly soon. On the other hand, if a patient wants to reduce the size of his prostate, then 5-alpha-reductase inhibitors are the better choice.

**POPD:** *Is there a correlation between prostate gland size and symptoms?*

**SANDA:** Well, that's an interesting question, because the studies that have looked carefully at that issue have not found a great deal of correlation between prostate size and symptoms. But as Kevin mentioned, the size of the prostate helps determine whether a 5-alpha-reductase inhibitor has any role or not.

In my practice, I generally recommend alpha-1 blockers as the first line of treatment because of the immediacy of effect. And although the effectiveness of 5-alpha-reductase inhibitors is limited to men with large prostates, the converse is not true. In other words, alpha-1 blockers seem just as effective in men with larger prostates as in those with smaller prostates. So they have a broad spectrum of action, which is another reason why I tend to recommend alpha-1 blockers as a first-line therapy. I reserve 5-alpha-reductase inhibitors for those patients who, for one reason or another, do not get sufficient symptom relief from an alpha-1 blocker, and who have a large prostate, are not in an emergency situation, and have the patience to wait for several months before the medication takes effect.

### Deciding which alpha-1 blockers are best

**POPD:** *Do you prescribe the nonselective alpha-1 blockers anymore? Or just the selective alpha-1 blockers?*

**SANDA:** The clear advantage of the selective alpha-1 blockers is that they are simpler to use and they take effect more quickly, because you don't have to worry about titrating the dose. The first-generation nonselective drugs have to be titrated gradually. How long that takes depends on how much the drug affects that particular person's blood pressure, and that's quite variable. Some patients can reach a therapeutic dose of terazosin or doxazosin almost immediately without much effect on their blood pressure, but others need the dose increased much more slowly.

I also try to avoid the nonselective drugs because of their impact on blood pressure, but if I do prescribe them, I advise patients that if they

**In brief:** Two types of alpha-1 blockers are available. The first generation, nonselective alpha-1 blockers—doxazosin (Cardura) and terazosin (Hytrin)—affect not only the prostate but the heart and blood vessels, and so have an impact on blood pressure. The second generation, selective alpha-1 blockers—alfuzosin (Uroxatral) and tamsulosin (Flomax)—mainly affect the prostate, and so have less of an impact on blood pressure, but sometimes create ejaculation difficulties.

experience lightheadedness and fatigue, or just feel washed out, that might indicate that their blood pressure is being affected too drastically by the medicine.

**MORGENTALER:** I'm so glad that we have the newer selective alpha-1 blockers because I've found that titrating of doses is very confusing for patients. There are certainly times when the nonselective alpha-1 blockers might be useful, but there's no question in my mind that the new medications that generally have a single dose are simpler to prescribe, simpler to explain, and simpler for the patients to take.

**LOUGHLIN:** I agree. A single-dose regimen is easier for the patient. If you ask someone who's in his 80s and who's already on six or seven other medications to titrate an alpha-1 blocker, you're just asking for a drug error.

**MORGENTALER:** I do prescribe the nonselective drugs for men if they've been on one of the drugs for a long time and they've been satisfied with it; then I'll just renew the prescription. A second issue is cost. Every now and again there are some formulary issues, where a health plan will only cover the nonselective alpha-1 blockers because they are less expensive.

**SANDA:** If cost is a concern, then I mention that both of the nonselective alpha-1 blockers are available in generic forms, which are cheaper than the prescription drugs. (See Table 4, page 33.)

#### Side effects of alpha-1 blockers

**In brief:** The main concern about the nonselective alpha-1 blockers is that they may cause orthostatic hypotension when used in conjunction with other blood pressure medications or erectile dysfunction drugs. But the selective alpha-1 blockers are apparently more likely to cause ejaculatory difficulties.

**POPD:** *How do you advise patients who are taking antihypertensives?*

**SANDA:** Certainly with the nonselective alpha-1 blockers there's a great concern in terms of adjusting other antihypertensives. I think it's much less of a concern with the selective alpha-1 blockers, such as Flomax.

**MORGENTALER:** The one big issue that comes up with men who are on Flomax, although it can happen on any of the alpha-1 blockers, is the issue of ejaculatory dysfunction. This hasn't shown up so much in the studies, or in the manufacturer's materials, but we hear a lot about it from patients. Some men aren't bothered at all, but others are really affected a lot.

**POPD:** *Is ejaculatory dysfunction just a problem for the selective alpha-1 blockers, or do you also see it with the nonselective ones?*

**MORGENTALER:** This problem may have happened occasionally in men taking Cardura and Hytrin, but the complaints really increased when Flomax came out. I mean, it's fairly routine now to have a patient talk to me about this problem. They say things like, "Doc, I have an orgasm and nothing comes out. There must be something terribly wrong with me." I find that if men are aware of this possibility ahead of time, so that they can anticipate it,

**Table 5. General guidelines for BPH medications**

<b>Medication and mechanism of action</b>	<b>Potential side effects</b>	<b>You might want to consider using if</b>	<b>You may not want to use if</b>
<p><b>Alpha-1 blockers (nonselective)</b> doxazosin (Cardura, generic) terazosin (Hytrin, generic)</p> <p><b>How they work</b></p> <ul style="list-style-type: none"> <li>Relax smooth muscles in the urinary tract, allowing urine to flow more freely</li> <li>Also affect other smooth muscles throughout the body</li> </ul>	<ul style="list-style-type: none"> <li>Dizziness, headache, and fatigue (most common)</li> <li>Nasal congestion, dry mouth, and swelling in the ankles (occasional)</li> <li>Retrograde ejaculation and other ejaculatory problems (occasional)</li> <li>Hypotension (low blood pressure); may pose a danger for some men (rare)</li> </ul>	<ul style="list-style-type: none"> <li>You have a normal to moderately enlarged prostate (under 35 grams)</li> <li>Cost is a consideration (these drugs are available in generic forms)</li> <li>You want something with a proven track record that works within weeks</li> <li>You have mild hypertension and want to reduce blood pressure while also treating BPH</li> </ul>	<ul style="list-style-type: none"> <li>You suffer frequent urinary tract infections</li> <li>You have severe BPH</li> <li>You have hypertension or heart disease (check with your doctor about mixing medications)</li> </ul>
<p><b>Alpha-1 blockers (selective)</b> alfuzosin (Uroxatral) tamsulosin (Flomax)</p> <p><b>How they work</b></p> <ul style="list-style-type: none"> <li>Relax smooth muscles in the urinary tract, allowing urine to flow more freely</li> <li>Act more selectively on muscles in the urinary tract than elsewhere</li> </ul>	<ul style="list-style-type: none"> <li>Dizziness, headache, and fatigue (most common)</li> <li>Nasal congestion, dry mouth, and swelling in the ankles (occasional)</li> <li>Retrograde ejaculation (may occur with tamsulosin; less likely with alfuzosin)</li> <li>Erectile dysfunction (possible but less likely than with 5-alpha-reductase inhibitors)</li> </ul>	<ul style="list-style-type: none"> <li>You have a normal to moderately enlarged prostate (under 35 grams)</li> <li>You are taking a medication for hypertension and want to use an alpha-1 blocker</li> <li>You are concerned about diminished ejaculation (less likely with alfuzosin)</li> </ul>	<ul style="list-style-type: none"> <li>You suffer frequent urinary tract infections</li> <li>You have severe BPH</li> </ul>
<p><b>5-alpha-reductase inhibitors</b> dutasteride (Avodart) finasteride (Proscar)</p> <p><b>How they work</b></p> <ul style="list-style-type: none"> <li>Reduce the size of the prostate, easing pressure on the urethra and allowing greater urine flow</li> <li>Prevent the conversion of testosterone into dihydrotestosterone (DHT), which stimulates prostate growth</li> </ul>	<ul style="list-style-type: none"> <li>Decreased libido (occasional)</li> <li>Decreased volume of ejaculate (occasional)</li> <li>Erectile dysfunction (occasional)</li> <li>Gynecomastia (rare)</li> </ul>	<ul style="list-style-type: none"> <li>You have a large prostate (more than 55 grams)</li> <li>You want to avoid surgery (these drugs reduce the likelihood)</li> <li>You are patient (the drugs may take at least six months to act, and up to two years to show full benefits)</li> <li>You want to reduce your overall risk of prostate cancer (but see caveat, next column)</li> </ul>	<ul style="list-style-type: none"> <li>You are concerned about your risk for aggressive prostate cancer (finasteride may increase this risk)</li> <li>Cost is a consideration (both drugs are expensive and not yet available as generics)</li> </ul>

they can deal with it. But when a man isn't prepared, and when he's still very interested in his sexuality, and his definition of potency includes ejaculatory potency, then it can become a problem.

**POPD:** *Uroxatral is supposed to cause less ejaculatory disturbances. Have you found that to be the case?*

**MORGENTALER:** I personally have very little experience so far with Uroxatral. The data suggest that it's not as much of a problem as it is with Flomax, but it's still there.

**LOUGHLIN:** I also tend to prescribe far more Flomax than Uroxatral, but that's probably because Flomax has been around longer and my patients have been satisfied with it. But I think they're probably about the same in terms of efficacy.

**POPD:** *Are there any other key side effects that you see in people who take alpha-1 blockers for years?*

**MORGENTALER:** Every medication has risks, but over all, these medications are remarkably safe. The one thing that I do hear from patients, and it does show up in the literature as well, is that some people just don't tolerate these medicines well. They feel lousy, weak, they don't feel like themselves. But I think the number of men who experience that is fairly small.

**POPD:** *And what do you do in those circumstances?*

**MORGENTALER:** Whenever I give a patient a medication, I try to alert him to the most common side effects. And I also tell him, you know, some guys just don't tolerate certain kinds of medicine, and so you may feel weak or lousy. If it only lasts for a day or two, I advise them to try and get through it, but if they feel awful or the discomfort persists, I ask them to stop the medication and give me a call, and we can try something else.

### Using BPH and erectile dysfunction drugs

**In brief:** Many men who are taking alpha-1 blockers for BPH are also taking erectile dysfunction medications, known as PDE-5 inhibitors. The FDA has approved three: sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra). Because these medications widen arteries throughout the body, the concern has been that if they are mixed with alpha-1 blockers, they may cause a precipitous drop in blood pressure.

**POPD:** *The common wisdom is that it's not safe to mix PDE-5 inhibitors with alpha-1 blockers. Is that really the case?*

**MORGENTALER:** I would say that, in my experience, the concern about combining alpha-1 blockers and PDE-5 inhibitors has lessened. Even the FDA has softened its cautionary language (see "What the FDA advises," page 43).

**LOUGHLIN:** Most urologists today advise patients to take these medications at different times during the day rather than simultaneously. There's not great compelling evidence that if you take them simultaneously anything terrible would happen, but it's wise to be cautious.

**POPD:** *So do you recommend taking the alpha-1 blocker in the morning and the erectile dysfunction drug in the evening?*

**MORGENTALER:** Frankly, I don't. I've been prescribing these medicines since Viagra came out in 1998, and I've never seen a single problem of hypotension from the combination. I think this is an issue that really has no substance to it.

**SANDA:** If a patient who is on an alpha-1 blocker is also using Viagra or another PDE-5 inhibitor, I mention that there have been some reports of interactions, but that I've never encountered it in my practice and that I don't know of any of my colleagues who have. I personally feel that it's quite safe for people to use both types of drugs at once.

#### Other concerns about alpha-1 blockers

**POPD:** *Do you believe there is the potential to aggravate BPH symptoms or urinary retention if your patients take over-the-counter medicines such as Sudafed during cold and flu season? And what are your thoughts about herbal and over-the-counter remedies?*

**SANDA:** I've certainly encountered many men who have gone into urinary retention while taking over-the-counter cold remedies. I think it's important for any man with BPH, whether or not he's being treated, to be aware that medications for nasal congestion can exacerbate urinary problems and could potentially lead to acute urinary retention. To avoid problems, I advise patients to pay attention to any changes in urination while they are taking Sudafed or similar agents.

**LOUGHLIN:** Another thing men with BPH may want to be aware of is that there are a lot of people out there who still take saw palmetto and swear by it, and I think it's important to say that the best study done on saw palmetto, which was published in the *New England Journal of Medicine*, found that it's no better than placebo (see "How effective is saw palmetto?" on page 44).

Most herbal therapies do appear to be safe. But they are not FDA-regulated. A lot of patients don't consider herbal remedies to be drugs, and technically

**In brief:** Alpha-1 blockers can cause other types of side effects and interact with other medications and herbal remedies.

#### What the FDA advises

The current FDA labels include the following instructions about how to take these PDE-5 inhibitors when also taking an alpha blocker:

**Sildenafil (Viagra):** To reduce your risk of becoming dizzy or fainting, your doctor may advise you start by taking the lowest dose. *FDA, June 2006*

**Tadalafil (Cialis):** To reduce risk of fainting, begin taking it at the lowest possible dose. *FDA, August 2005*

**Vardenafil (Levitra):** To minimize risk of fainting, start medication at the lowest possible dose. *FDA, July 2005*

**How effective is saw palmetto?**

In an effort to determine how well saw palmetto reduces symptoms of BPH, researchers randomly assigned 225 men over age 49 with moderate to severe BPH symptoms to one of two groups. One group took 160 mg of saw palmetto extract twice a day; the other received a placebo. At the end of one year, there was no significant difference in the two groups in symptoms such as prostate size, PSA level, or maximal urinary flow.

SOURCE: Bent S, Kane C, Shinohara K, et al. Saw Palmetto for Benign Prostatic Hyperplasia. *New England Journal of Medicine* 2006;354:557–66). PMID: 16467543.

they're not, but sometimes they interact with medications. If you are taking an herbal remedy, it's important that you mention it to your doctor.

**SANDA:** I probably take an even stronger stance. On the one hand, I certainly tell patients that if they're on herbal remedies, I can accept that and that's okay, but I do like to mention the PC-SPES story, and the reality that there are herbal medications that have been used for prostate conditions in the past, but when they were evaluated more rigorously were found to actually be dangerous to patients. [*Editor's note: PC-SPES was pulled from the market because of concerns about contamination.*] The real issue is that the danger wasn't evident for many years while those formulations were being used by many people. I think men need to be aware that there is the potential for hidden dangers in those herbal remedies and probably a greater potential among those than there is among the FDA-approved drugs.

**5-alpha-reductase inhibitors**

**In brief:** Two 5-alpha-reductase inhibitors are on the market: dutasteride (Avodart) and finasteride (Proscar). Because both of these drugs work by affecting levels of male hormones in the prostate, they may have sexual side effects. Although uncommon, these can be devastating when they occur.

**POPD:** *Do you recommend one 5-alpha-reductase inhibitor more than the other?*

**LOUGHLIN:** At this point, there's no evidence that one or the other is superior. There are studies ongoing to see whether that may be true, but I think from a patient's point of view, there's no evidence that Proscar is better than Avodart or vice versa.

**POPD:** *What kind of side effects do you see with the 5-alpha-reductase inhibitors?*

**LOUGHLIN:** Both can cause gynecomastia [*enlargement of the breasts in men*]. It doesn't happen in a large percentage of patients, but some men are extremely bothered by it, and I think it's something that's important to tell a patient before he starts taking one of these drugs.

**POPD:** *Is there any way to identify men who are more likely to develop this problem?*

**LOUGHLIN:** Unfortunately, no. And when you stop taking a 5-alpha-reductase inhibitor, in my experience, the gynecomastia does not always go away. So

it happens in a small percentage of men, but when it does happen, it can be bothersome. I can remember at least one man whom we actually had to refer to a plastic surgeon to talk about having breast reduction surgery.

**SANDA:** It's not one of the more common problems, but it can happen. What I've encountered more often are complaints about reduced ejaculate volume, and physical changes such as diminishment in the size of the flaccid penis.

**MORGENTALER:** I do a lot of research on testosterone, and gynecomastia can be a sign of low testosterone. So it may be that the 5-alpha-reductase inhibitors cause gynecomastia because of their effect on testosterone.

But I actually can't remember ever seeing anybody on Proscar or Avodart in my practice who developed gynecomastia, although clearly it happens. I just don't remember seeing it. It must be relatively uncommon. This probably develops in men who are somehow predisposed to it. It can be treated by plastic surgery or in some cases, radiation.

### 5-alpha-reductase inhibitors, prostate cancer, and PSA

**POPD:** *What did you think of the Prostate Cancer Prevention Trial (PCPT) and what it means for patients taking one of the 5-alpha-reductase inhibitors?*

**LOUGHLIN:** The study is interesting, certainly, but we don't have the final answer yet about whether Proscar really does decrease the risk of cancer. I think the honest assessment at this point is that the study has raised the possibility of this effect, and it's being actively investigated, but we don't have a resolution of that question yet. So, that's something that readers need to be aware of and they need to talk about with their urologist.

**MORGENTALER:** You know, it's a fascinating study. On the one hand, taking Proscar caused a remarkable reduction in prostate cancer, a 25% reduction. I mean, we would hope for treatments for other kinds of conditions that would have the success rate as good as that. And yet at the same time it looks as if taking Proscar increased the cancers that probably are the most worrisome in terms of mortality and morbidity, so it's really hard to know what to make of that.

I personally don't use finasteride or 5-alpha-reductase inhibitors for prevention. I don't know too many doctors who do.

**SANDA:** It clearly hasn't caught on, precisely because of the concerns about the downside—of whether increasing the risk of developing an aggressive cancer outweighs the possible benefit of reducing overall risk of cancer.

**LOUGHLIN:** Although if we're talking about monitoring risk, anyone taking a 5-alpha-reductase inhibitor should be aware that it will change their PSA level. Generally speaking, after a man has been on a 5-alpha-reductase inhibitor for several months, his PSA should decrease by half. And then you

**In brief:** The PCPT found that men who took one of the 5-alpha-reductase inhibitors—finasteride (Proscar)—reduced their risk of developing prostate cancer by nearly 25%. However, if they did develop prostate cancer, it tended to be the more aggressive kind (see Table 1, page 7).

can interpret that PSA as you would any other PSA by doubling it. Alpha-1 blockers don't affect PSA levels.

**MORGENTALER:** And even though the common wisdom is that you double the PSA once a man is on a 5-alpha-reductase inhibitor, it's important to point out that that's actually an average, and that not everybody is going to have his PSA reduced by half while on one of these medications. There are always differences with individuals, and when somebody's had a PSA level increase from 3 to 3.5, and then up to 4, and then we've put them on a 5-alpha-reductase inhibitor, some of those guys don't see their PSA levels go from 4 to 2. Some of them may go from 4 to 3, and some may go from 4 to 1. So it's important to establish a baseline PSA before you begin taking a 5-alpha-reductase inhibitor, and then get tested again after taking the medication for six months or so.

#### Acute urinary retention

**In brief:** Acute urinary retention occurs when someone is unable to urinate normally even though he has a strong urge. This is a medical emergency, because if the bladder is unable to excrete urine, over time it may cause pressure on the kidneys, possibly leading to kidney failure—which is life-threatening. A man who develops acute urinary retention usually has to go to the emergency room to have a catheter inserted so urine can exit the body.

**POPD:** *When you counsel patients, what do you tell them about avoiding problems with acute urinary retention? Is there any way for a man taking a BPH medication to avoid developing this problem while taking a plane trip or at a sporting event—where he may not have easy access to a toilet and need to hold in his urine?*

**LOUGHLIN:** Well, unfortunately, I don't think there's a clearly identifiable prodrome that says Mr. Jones is likely to go into retention during a plane trip while Mr. Smith isn't. We sometimes see this problem develop during a non-urologic surgical procedure, where they go into retention as a consequence of anesthesia.

**SANDA:** Usually there are no warning signs of who is going to go into retention. Of course, if the symptoms are increasing in severity, then it may well be a sign that the bladder is being damaged because of the obstruction. And you may be able to avoid problems by increasing the dose of your medication or changing your medication. So if the symptoms get worse, definitely contact your doctor. Make an adjustment.

**MORGENTALER:** As a rule, I do not speak to my patients about urinary retention if I'm treating them for BPH, unless there is something about their situation that sort of raises a red flag. If a man has an enormous prostate, if I have objective data like urine flows that are very weak or post-void residuals that are substantial, or I think that maybe a small additional insult may tip him over into retention, then I might discuss some options with him. But I think it's important to recognize that urinary retention can happen even in the absence of a prostate: It happens to women. And it sometimes happens after people receive certain anesthetics, if they're on narcotics, if they're older, or if they become constipated.

### Combination medical therapy

**POPD:** *When do you recommend combination therapy for someone with BPH?*

**LOUGHLIN:** The Medical Therapy of Prostatic Symptoms (MTOPS) study showed that combination therapy clearly has a role. Obviously, these two classes of drugs have different mechanisms of action, so if you use both drugs simultaneously, chances are you'll have a higher response rate. The downside is that the cost is increased when you're using two drugs, and each type of drug has its own side effect profile, so you may increase the likelihood of experiencing side effects.

We usually don't start off with combination therapy. But if one of my patients has a large prostate gland and yet is eager to see results soon, then sometimes I simultaneously prescribe both an alpha-1 blocker and a 5-alpha-reductase inhibitor, with the plan to drop the alpha-1 blocker in six months or so, once the other medication has begun to show results. That's a reasonable strategy for some men. ♥

**In brief:** The MTOPS study, reported in the *New England Journal of Medicine* in 2003, provided evidence that taking a combination of an alpha-1 blocker and a 5-alpha-reductase inhibitor reduced the chance of BPH symptoms worsening more significantly than taking either medication alone (see "Combination therapy," page 30, for more information about this study). But questions remain about which patients are best served by combination therapy.



## Searching PubMed in five easy steps

You can find and read the studies that are referenced in the pages of *Perspectives on Prostate Disease* by searching PubMed, a resource of the National Library of Medicine. The abstracts (short summaries) of the studies are available for free, but in many cases you will have to pay to obtain the full report.

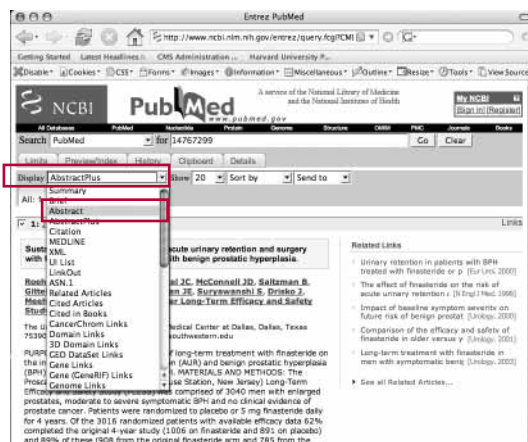
Here's how to access an abstract:

1. Open up your browser's window while connected to the Internet. Type [www.pubmed.gov](http://www.pubmed.gov) and hit return.
2. This brings you to the PubMed welcome page. You will see the following:

Search PubMed for Go Clear



3. In the space after "for," type the PMID (short for "PubMed ID") number that appears with the reference you want. For example, for the first Prostate Cancer Prevention Trial study referenced on page 6, the PMID is 12824459.
4. Click on "Go" or press the enter key. PubMed will retrieve the abstract, which will appear on your screen.
5. To purchase an article (if this option is available), change "Display" from "AbstractPlus" to "Abstract" (click on the arrow to pull down the menu). If the journal provides a link for purchase—or if a link is provided for a free copy of the article—click on the icon and follow the instructions.



## Glossary

**acute urinary retention:** An inability to squeeze any urine past the enlarged prostate.

**benign prostatic hyperplasia (BPH):** Enlargement of the prostate gland, usually developing with age. It may be associated with an elevated PSA, but there is no cancer present in the gland.

**biochemical recurrence:** A post-treatment increase in PSA level, indicating that prostate cancer has recurred or spread.

**biopsy:** A procedure for obtaining samples of tissue to determine the presence or absence of disease or cancer. It can be done using a needle or as a surgical procedure.

**cancer:** The presence of abnormal or malignant cells that have lost normal regulatory controls of growth; cancer cells may also spread to other parts of the body and grow.

**core:** A piece of tissue obtained during a biopsy procedure.

**differentiation:** A term used to describe the normal process of cell development; applied to cancer, it describes how closely the cancer does or does not resemble the organ from which it originated.

**digital rectal examination (DRE):** A part of the physical examination in which the physician puts a gloved finger into the rectum and examines the prostate gland and rectum for abnormalities that can be detected by touch.

**erectile dysfunction:** A more specific term for impotence that refers to the inability to have and to maintain an erection sufficient for intercourse.

**Gleason score:** A system of identifying and grading the appearance of prostate cancer, as viewed under the microscope. Scores range from 2 to 10.

**gynecomastia:** Breast enlargement occurring in men.

**hydronephrosis:** Distention of the kidney with urine, occurring when the ureters are blocked.

**impotence:** The inability to obtain or maintain an erection sufficient for sexual intercourse; also called erectile dysfunction.

**localized:** When used alone or with the term cancer, refers to cancer that is limited to a specific gland, without any distant spread; an organ-confined cancer.

**lymph nodes:** Small specialized clusters of tissues that help fight infections; they may contain cancer cells that have moved out of a given tissue or organ.

**margin:** In reference to the prostate gland, the outermost surface of the gland, which is removed at the time of radical prostatectomy.

**metastatic:** When used alone or with the term cancer, refers to cancer that has spread throughout the body, beyond the organ or tissue in which it originated.

**micrometastases:** Cancer cells outside the primary tumor, such as in the lymph nodes, that are still too small to be detected by CT or bone scan or by physical examination.

**neurovascular bundle:** That portion of the prostate gland that contains the nerves and blood vessels necessary for the maintenance of erectile functioning and potency.

**orthostatic hypotension:** An abnormally low blood pressure, dizziness, and lightheadedness.

**perineum:** The area between the bottom of the scrotum and the anus.

**placebo:** A pill with no active ingredients, or a “dummy” treatment.

**post-void residual:** The amount of urine left in the bladder after urinating.

**prodrome:** An early symptom indicating a disease is developing.

**prognosis:** The prediction of how well the patient is likely to do (with or without treatment of the disease), as estimated from symptoms, pathology, and other diagnostic information.

**progression:** The increase in symptoms of a disease, such as BPH, or the growth and spread of cancer, either by direct extension or metastases.

**prostate gland:** A walnut-shaped gland at the base of the bladder in males, involved in reproductive functioning.

**prostate-specific antigen (PSA):** A substance secreted by the prostate gland, some of which passes into the bloodstream. It can be abnormally elevated in patients with prostate cancer, benign enlargement of the prostate (BPH), or other conditions.

**prostatitis:** An infection of the prostate gland, usually by bacteria; this noncancerous condition can raise the PSA level.

**proteinuria:** Excessive amounts of protein in the urine, a sign that kidney function may be impaired.

**seminal vesicles:** Structures surrounding the prostate gland involved in storing and screening the prostate gland secretions.

**stage of cancer:** The level of advancement of cancer. The three general stages are localized, regional, or disseminated (or metastatic). Specific stages may be identified by number (I, II, III) or letter (A, B, C, D).

**testosterone:** An androgen; a male hormone involved in the growth and development of the prostate gland and prostate cancer.

**titrating:** Increasing the dosage of a medication to an effective range over a period of days or weeks.



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