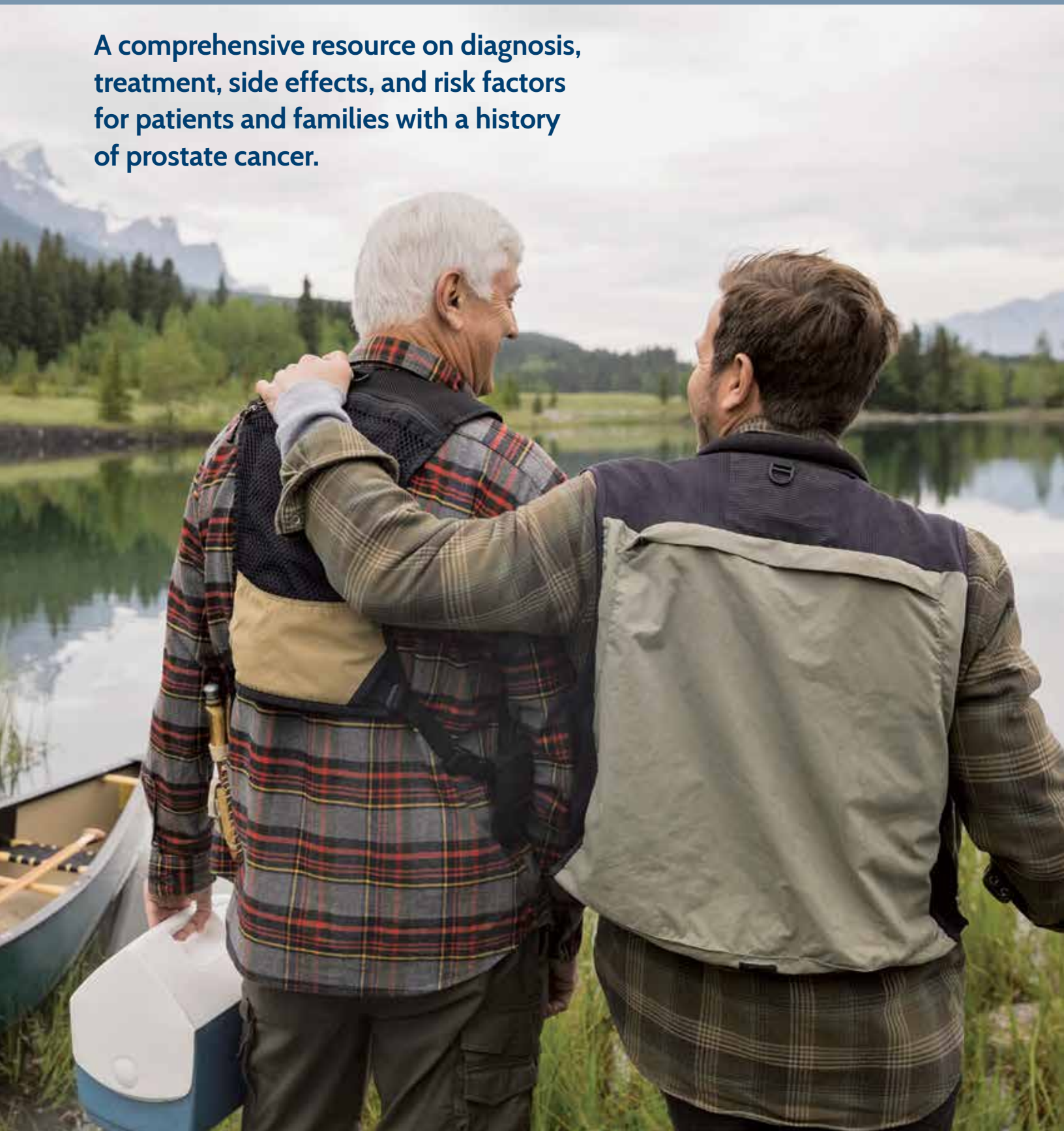


PROSTATE CANCER

PATIENT GUIDE

A comprehensive resource on diagnosis, treatment, side effects, and risk factors for patients and families with a history of prostate cancer.



**“Be vigilant, live healthy,
and don’t give up. This disease
can be conquered.”**

— FORMER COMBAT MARINE, KOREAN WAR

About this guide

There are no two ways about it: getting diagnosed with cancer is hard and it is life-changing. Despite increasing optimism about treatment, today's cancer landscape can be challenging as patients have access to an unprecedented amount of information. There are literally millions of cancer-related webpages, blogs, and videos available at your fingertips. But it's important to acknowledge that this isn't always a helpful thing. A cancer diagnosis can be disorienting, and for many, the overwhelming volume of information available can be more of a burden than an aid.

This guide focuses all of the information available about contemporary prostate cancer research, treatment, and lifestyle factors into one consolidated resource. It is for any man who has been newly diagnosed, who is in treatment, or is concerned about a rising PSA. Beyond that, it's for any loved one or caregiver who wants to cut through the information noise and get directly to need-to-know information for prostate cancer patient navigation. Lastly, as we are beginning to recognize the genetic underpinnings of cancer, this guide is for any family member who might want to understand how their shared genes affect their own short- and long-term risks factors—and whether they should be screened as well.

We gratefully acknowledge the contributions of Daniel Spratt, MD (University of Michigan), Andrew Armstrong, MD (Duke University), Andrea Miyahira, PhD (Prostate Cancer Foundation), Heather Cheng, MD, PhD (University of Washington; Fred Hutchinson Cancer Research Center), Bill Curry, Izak Faena, MD (University of California, Los Angeles), Stacy Loeb, MD, MSc (New York University), Alicia Morgans, MD (Northwestern University), Christopher Sweeney, MBBS (Dana-Farber Cancer Institute; Harvard Medical School), Howard Soule, PhD (Prostate Cancer Foundation) and Skip Holden, MD (Prostate Cancer Foundation), Jonathan Simons, MD (Prostate Cancer Foundation), Julie DiBiase, PhD (Prostate Cancer Foundation).

This guide was produced in 2017 by the Prostate Cancer Foundation (PCF). The Prostate Cancer Foundation is the world's leading philanthropic organization funding and accelerating prostate cancer research. Since being founded in 1993, the Prostate Cancer Foundation has funded key research leading to many of the treatments used by doctors today to improve the lives of patients, with the mission that someday, soon, no man will die of this disease.

Subjects depicted are models and are used for illustrative purposes only. Prostate cancer standards of practice change regularly. For the most up-to-date information, please register for updates at www.pcf.org.

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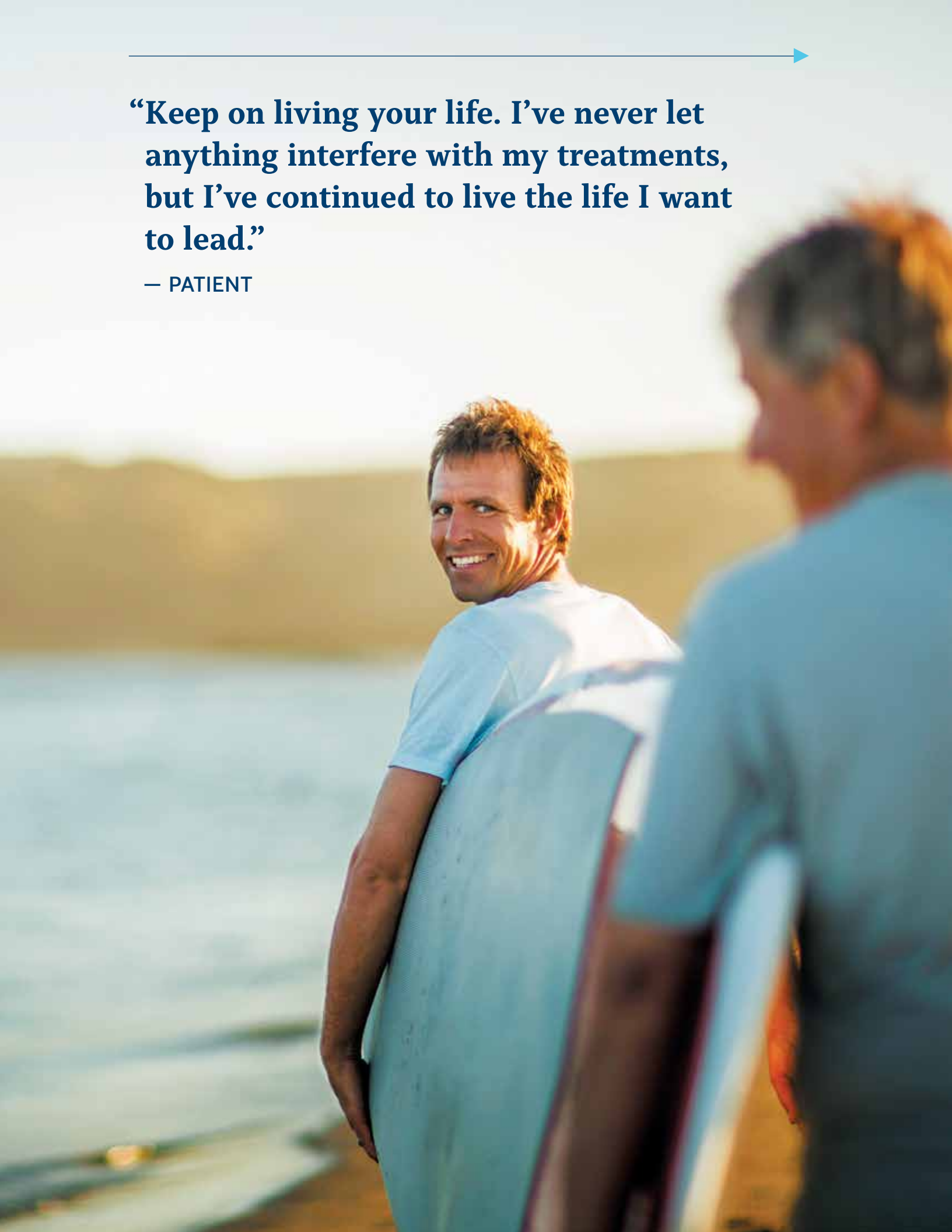
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“Keep on living your life. I’ve never let anything interfere with my treatments, but I’ve continued to live the life I want to lead.”

— PATIENT



GENERAL INFORMATION

What is Prostate Cancer?

In general, cancer is a condition in which a normal cell becomes abnormal and starts to grow uncontrollably without having the signals or “brakes” that stop typical cell growth. Prostate cancer starts in the prostate gland, a small gland located below the bladder, that is responsible for secreting one of the components of semen. Prostate cancer cells form masses of abnormal cells known as tumors.

Prostate cancer, therefore, is when a normal prostate cell becomes altered and starts growing in an uncontrolled way.

In many cases, prostate cancer is relatively slow-growing, which means that it takes a number of years to become large enough to be detectable, and even longer to spread outside the prostate, or metastasize. However, some cases are more aggressive and need more urgent treatment.

Surviving Prostate Cancer

Approximately 95% of all prostate cancers are detected when the cancer is confined to the prostate, so treatment success rates are high compared to most other types of cancer in the body. **The 5-year survival rate in the United States for men diagnosed with prostate cancer is 99%.** In other words, the chances of the cancer spreading or men dying from their prostate cancer is generally low. However, prostate cancer comes in many forms and some men can have aggressive prostate cancer even when it appears to be confined to the prostate.

Amidst so much optimism and progress in the last 10 years, it's important to keep in mind that prostate cancer is still a deadly disease for some men, and it is the second leading cause of cancer death among men in the US, with nearly 88 men dying from it every day.

In general, the earlier the cancer is caught and treated, the more likely the patient will remain disease-free. In fact, many men with “low-risk” tumors, which are the most common type of prostate cancer, can safely undergo Active Surveillance, in which they are monitored without immediate treatment (and treatment-related side effects) while still preserving their chance of long-term survival if the cancer becomes aggressive enough to require treatment.

Rates of Diagnosis

Prostate cancer is the leading cause of non-skin cancer in the US, and the second leading cause of cancer worldwide; approximately 1 in 8 men will be diagnosed with prostate cancer at some point in their lives. The older you are, the more likely you are to be diagnosed with prostate cancer.

Although only about 1 in 350 men under age 50 will be diagnosed, the rate shoots up to 1 in 52 for ages 50 to 59, 1 in 19 for ages 60 to 69, and 1 in 11 for men 70 and older. Nearly 60% of all prostate cancers are diagnosed in men over the age of 65.

IS THERE A CURE FOR PROSTATE CANCER?

When people think about cancer treatment success, they often think of the word “cure.” Sometimes statisticians think of “cure” as a function of time: is 5 years without a cancer recurrence equal to a cure? Or is it 10 years? Unfortunately, in some men, prostate cancers can recur even 10 years after treatment. So instead of using the term “cure,” doctors commonly use terms such as *biochemical control* (PSA levels kept at bay with medication) or *freedom from developing metastatic disease* (the cancer has not spread to distant organs) to help quantify the success of prostate cancer treatment.

17 genes

that run in families have been discovered that have overlap from prostate cancer to other cancers.



Since 1993, deaths from prostate cancer have been cut in half.



If the prostate cancer is caught at an early stage, most men will not experience any symptoms.

100%

Prostate cancer is 100% treatable if detected early.

Prostate cancer has one of the highest survival rates of any cancer.

10 THINGS TO KNOW

A man of African descent is 70% more likely to develop prostate cancer.

70%

As men age, their risk of developing prostate cancer increases exponentially.

Thanks to emerging science, in the next 5 years, we may see an end to all incurable prostate cancer.



Prostate cancer is the **most common** non-skin cancer in America.

2x

Men with relatives with a history of prostate cancer are twice as likely to develop the disease.

Prostate cancer is diagnosed with a biopsy. The most common reason for a man to undergo a prostate biopsy is due to an elevated prostate-specific antigen level, or PSA, determined by a blood test. Recent changes in PSA screening recommendations have impacted the rates of prostate cancer diagnosis (see Screening for Prostate Cancer, page 63).

Risk Factors

As indicated by the rates of diagnosis, **age** is the biggest—but not the only—risk factor for prostate cancer. Other important factors include family history, genetic factors, race, and lifestyle and dietary habits.

Genes for disease can run in families. Men who have a relative with prostate cancer are twice as likely to develop the disease, while those with 2 or more relatives are nearly 4 times as likely to be diagnosed. The risk is even higher if the affected family members were diagnosed before age 65. Men may also be at increased risk of prostate cancer if they have a strong family history of other cancers, such as breast cancer, ovarian cancer, colon cancer, or pancreatic cancer. Because family members share many genes, there may be multiple genetic factors that contribute to the overall risk of prostate cancer in a family. However, there are also some individual genes that we now know increase the risk of prostate cancer, and men with these genes may need to be screened differently or consider changes in treatment.

It is still a scientific mystery, but African American men are 73% more likely to develop prostate cancer compared with white men, and 2.4 times more likely to die from the disease.

Although there is clearly a disproportionate number of African American men who are diagnosed with prostate cancer, the increased death rate from prostate cancer has been shown to be due in part to inequality in getting access to healthcare, insurance, PSA screening, appropriate treatment and follow-up, other simultaneous conditions or treatments, and other socioeconomic factors. There is ongoing research to try to identify

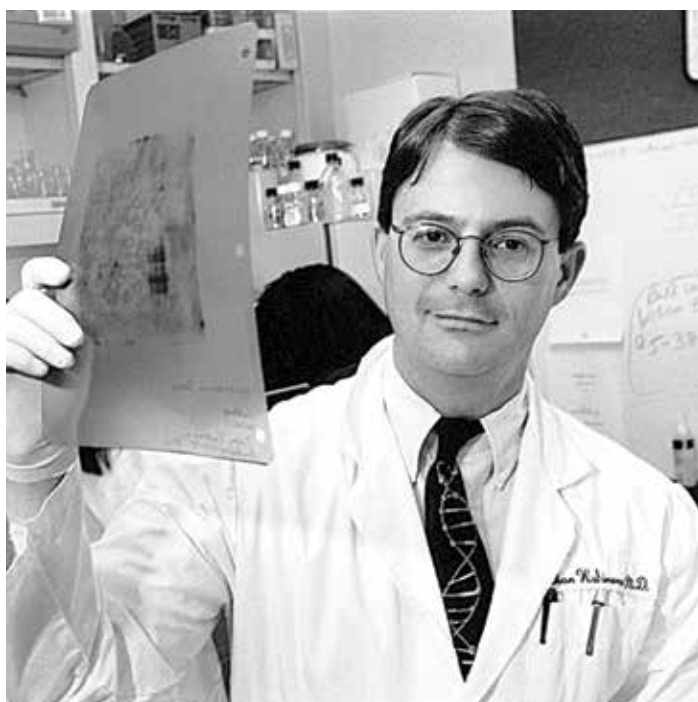
whether there are biological differences between cancers that develop in African American men so that we can improve treatment. It is also important to realize that not every African American man will get prostate cancer and that prostate cancer has a better chance of being managed effectively and cured if it is detected early.

Other risk factors for prostate cancer are social and environmental factors—particularly a high fat, high processed carbohydrate diet—and lifestyle. Men who are overweight or obese are at greater risk of ultimately developing an aggressive form of prostate cancer. Research has shown that in obese men, recovery from surgery tends to be longer and more difficult, and the risk of dying from prostate cancer can be higher.

Symptoms

If you've recently been diagnosed with prostate cancer, you may be asking yourself if there were warning signs or symptoms you should have noticed earlier. Unfortunately, there usually aren't any early warning signs for prostate cancer. The growing tumor does not push against anything to cause pain, so for many years the disease may be silent. That's why screening for prostate cancer is such an important topic for all men and their families. In rare cases, prostate cancer can cause symptoms that include:

- ▶ A need to urinate frequently, especially at night, sometimes urgently
- ▶ Difficulty starting or holding back urination
- ▶ Weak, dribbling, or interrupted flow of urine
- ▶ Painful or burning urination
- ▶ Difficulty in having an erection
- ▶ A decrease in the amount of fluid ejaculated
- ▶ Painful ejaculation
- ▶ Blood in the urine or semen
- ▶ Pressure or pain in the rectum
- ▶ Pain or stiffness in the lower back, hips, pelvis, or thighs



Dr. Jonathan Simons, CEO of the Prostate Cancer Foundation, was also one of its earliest grant recipients in 1994 as a young physician-scientist.

However, urinary symptoms don't necessarily mean you have cancer. Prostatitis or BPH (Benign Prostatic Hypertrophy, also known as enlargement of the prostate) are benign diseases but can cause similar symptoms and are very common.

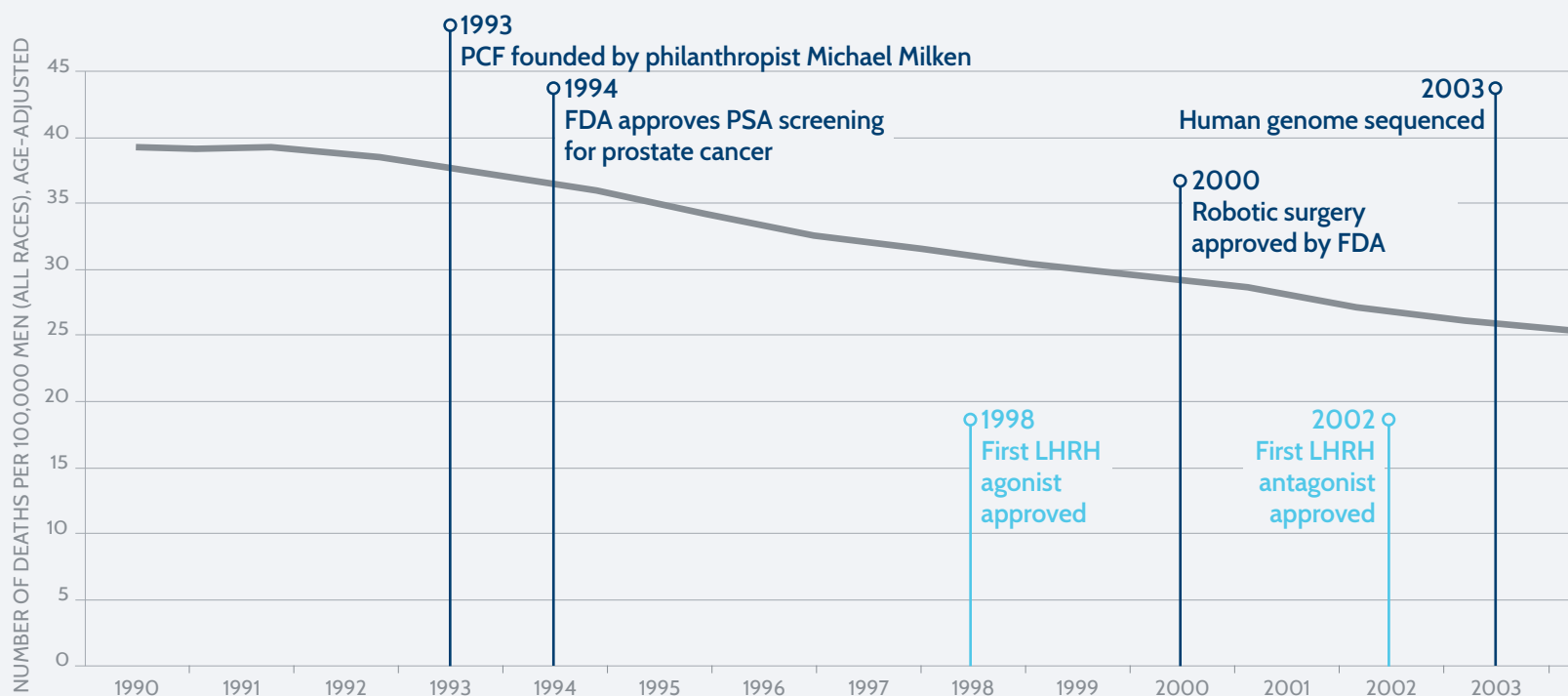
What about difficulty in having an erection? Again, this is most likely not caused by cancer but by other factors such as diabetes, smoking, cardiovascular disease, or just plain getting older.

Remember: Symptoms are symptoms, and no matter what's most likely to be causing them, you should get them checked out by a doctor.

History & Progress

Modern prostate cancer research was framed in the 1940s by the discovery that hormones, primarily testosterone, were responsible for the growth of tumors. Over the next 5 decades, various types of chemotherapy, radiation therapy, surgical options, and hormone therapy were refined.

Breakthroughs in Prostate Cancer Treatment and Practice



In 1994, the FDA approved the PSA (prostate-specific antigen) blood test to detect early prostate cancer in men without symptoms. Since cancer detected early is much easier to treat, use of the PSA test for cancer screening has contributed to the subsequent increase in the number of patients diagnosed early enough to be cured with surgery or radiation, and resulted in a 52% reduction of deaths from prostate cancer over the past 2 decades in the U.S. However, the PSA test sparked concerns that it has led to over-treatment of non-aggressive, slow-growing prostate cancers that would not have caused harm to the patient.

Since 1993 when the Prostate Cancer Foundation began funding life-prolonging advancements in research, amazing strides have been made in finding therapies for treating advanced prostate cancer that are now part of an improved standard of care. There have been tremendous advancements, including:

- ▶ Imaging technology to help find prostate cancer
- ▶ Precision radiation therapy
- ▶ Development of robotic surgery
- ▶ Numerous new FDA-approved therapies that help men live longer

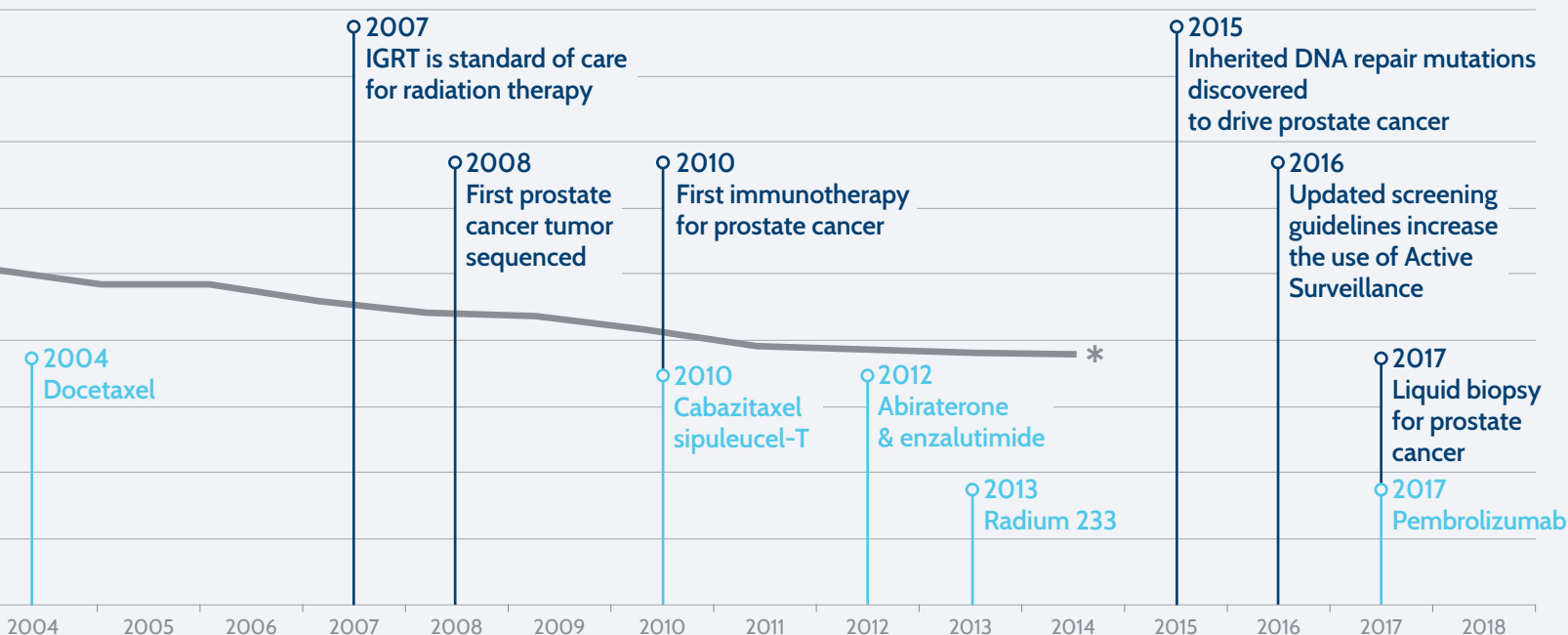
Because of these improvements and potentially other unknown factors, **since 1993, deaths from prostate cancer have been cut in half** (from 39.3 per 100,000 men in 1993, to 19.1 per 100,000 men in 2014).

Today, precision medicine, which involves looking at the DNA of your tumor and its unique genetic profile to match the right drug to the right patient at the right time, is ushering in a new era in treatment for prostate cancer that may someday lead to DNA testing as a gold standard in cancer care. Scientists are also exploring how immunotherapy—the process of using the body's own immune system to combat disease—can be used more effectively in treating prostate cancer.

MEDICAL BASICS

The more you know about the normal development and function of the prostate, where it's located, and what it's attached to, the better you can understand how prostate cancer develops and impacts a man's life over time—due either to cancer growth or as a result of treatment.

*Data available through 2014



The Anatomy of the Prostate

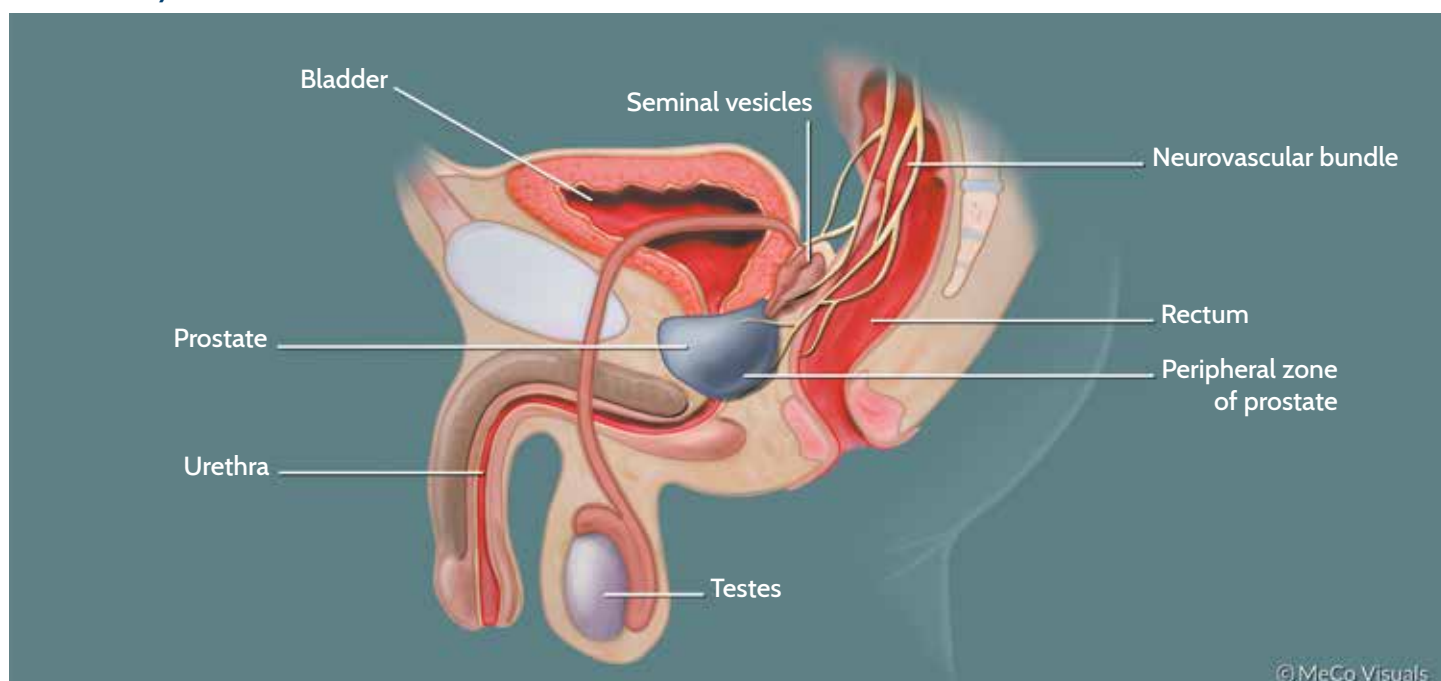
The prostate is a small, squishy gland about the size of a ping-pong ball. It sits under the bladder and in front of the rectum. The prostate is only present in men and is important for reproduction, because it supplies the fluids needed for sperm to travel and survive (sperm is not made in the prostate; it is made in the testes).

The prostate is divided into several anatomic regions, or zones. Most prostate cancer starts in the peripheral zone (the back of the prostate) near the rectum. That's why examining the prostate via a gloved finger in the rectum, known as digital rectal exam (DRE), is a useful screening test.

The seminal vesicles are rabbit-eared structures that store and secrete a large portion of the ejaculate. These structures sit on top of the prostate.

The neurovascular bundle is a collection of nerves and vessels that run along each side of the prostate, helping to control erectile function. They are usually a short distance away from the prostate, but sometimes they attach to the prostate itself.

The Anatomy of the Prostate



The bladder is like a balloon that gets larger as it fills up, holding urine until the body is ready to void. The urethra, a narrow tube that connects to the bladder, runs through the middle of the prostate and along the length of the penis, carrying both urine and semen out of the body. It is the hose that drains the bladder.

The rectum is the lower end of your intestines that connects to the anus, and it sits right behind the prostate.

The Biology of Prostate Cancer

To properly understand diagnosis and treatment options, it's important to understand how prostate cancer grows. A normal prostate uses androgens (including testosterone and dihydrotestosterone, or DHT) during its development and everyday function.

Once prostate cancer forms it feeds on androgens and uses them as fuel for growth. This is why one of the backbones of treatment for men, especially with advanced prostate cancer, is to lower a man's androgen levels with drugs collectively termed "hormone therapy."

Prostate cancer occurs when a normal prostate cell begins to grow out of control. In many cases, prostate cancer is a slow-growing cancer that does not progress outside of the prostate gland before the time of diagnosis.

ANDROGENS

Androgens are hormones that are important for many male characteristics and aspects of reproduction.

GRADE

Grade is a measure of how abnormal the prostate cancer cells look under the microscope. It's used to predict how quickly they might grow or spread.

QUESTION

If my doctor tells me that I have prostate cancer metastases in my bones or my lungs, does that mean I have bone cancer or lung cancer?

ANSWER

No. This does not mean you have “bone cancer” or “lung cancer,” since these tumor cells came from the prostate and did not develop from bone or lung cells. Your treatment would be focused on prostate cancer rather than bone or lung cancer.

The rate of growth and spread of prostate cancer is reflected in the grade of the cancer, measured by either the Gleason score or the ISUP grade group classification.

Prostate cancers that are composed of very abnormal cells are much more likely to both divide and spread faster from the prostate to other regions of the body. Often, prostate cancer spreads first to tissues that are near the prostate, including the seminal vesicles and nearby lymph nodes.

Researchers have identified various biological and genetic subtypes of prostate cancer. Although these subtypes are typically not yet used to guide treatment recommendations, they are the subject of active research funded by the Prostate Cancer Foundation.

Understanding Metastasis

Sometimes cancer cells will escape the prostate and grow quickly, spreading to nearby tissue. Nearby lymph nodes are often the first destination for a spreading cancer. If prostate cancer has spread to your lymph nodes when it is diagnosed, it means that there is higher chance that it has spread to other areas of the body as well.

Metastasis refers to tumor cells leaving the prostate and forming tumors somewhere else in the body.

If and when prostate cancer cells gain access to the bloodstream, they can be deposited in various sites throughout the body, most commonly in bones, and more rarely to other organs such as the liver, lung, or brain. Bone metastases are seen in 85% to 90% of metastatic cases.

What is PSA?

PSA, or Prostate Specific Antigen, is a protein produced by the prostate and found mostly in the semen, with very small amounts released into the bloodstream. When there's a problem with the prostate—such as the development and growth of prostate cancer—more PSA is released. PSA eventually reaches a level where it can be easily detected in the blood. This is often the first indicator of prostate cancer.

During a PSA test, a small amount of blood is drawn from the arm, and the level of PSA is measured. Doctors look at the overall level of PSA, as well as its rate of rising (velocity) compared with prior test results. As the PSA number goes up, the chance that cancer is present increases. Men whose levels go above 3 or 4 are often recommended to undergo a biopsy; however, this PSA level does not mean that prostate cancer is definitely there, and some cancers may be present even when PSA levels are lower.

THE PSA DEBATE

The PSA is not a perfect test. Elevated levels can be caused by other benign prostate diseases and problems, such as BPH (benign prostatic hyperplasia, an enlarged prostate) or prostatitis (an infection in your prostate). There is an active debate around prostate cancer screening. Some health care professionals are concerned that increased PSA screening is finding many tumors so slow-growing as to be no threat to the patient, leading to “overtreatment,” and that many men with these low-risk cancers are getting treatments they do not need but that can have significant side effects. However, there is also data to support that PSA testing has reduced the death rate from prostate cancer, because men with aggressive cancers are diagnosed earlier, often before the cancer has spread, and can be cured and/or more effectively managed by earlier treatment.

PSA screening decisions should be made on a case-by-case basis between the doctor and patient, based on a full examination of risk factors.

Once a man has a confirmed diagnosis of prostate cancer, rising PSA is a useful test to track prostate cancer growth, since it can be detected well before any clinical signs or symptoms. The PSA is also widely accepted as an invaluable tool for monitoring prostate cancer disease activity and remission from prostate cancer after treatment.

The Biology of Sex Steroids

Prostate cancer cells are just like all other living organisms—they need fuel to grow and survive. The main fuel for prostate cancer growth is the sex hormone testosterone.

The term sex steroid, or sex hormone, refers to the substances secreted by the testes and ovaries, respectively androgens and estrogens, which are responsible for the function of the reproductive organs and the development of secondary sex characteristics (such as facial hair, muscle mass, and sex drive). Androgens and estrogens are present in both men and women, though at different levels. The most important androgen for male reproduction is testosterone. Testosterone is primarily made in the testes, but a smaller amount is made in the adrenal glands above the kidneys. The prostate typically grows during adolescence under the control of testosterone.

The prostate is not essential for life, but it is important for reproduction. It supplies substances that facilitate fertilization, sperm transit, and sperm survival. Enzymes like PSA (the same protein that is measured in the blood test) loosen up semen to help sperm reach the egg after intercourse. Sperm is made in the testes, and it travels through the prostate during its transit, picking up seminal fluid along the way.

Since androgens—including testosterone—fuel prostate cancer growth, prostate cancer treatment regimens may include some amount of hormone therapy, which deprives tumor cells of androgens.

The term “medical castration” refers to a drug treatment regimen that is used to control hormone levels. Androgen deprivation therapy (ADT), whereby medication is used to cut off the supply of testosterone to the prostate, is part of the treatment regimen for metastatic prostate cancer and also for some patients with non-metastatic disease. ADT is associated with high rates of response, and it can have side effects, especially when used for long durations of time (i.e. years). Of note, testosterone replacement therapy, which is prescribed for some men with low testosterone, has not been shown to increase the risk of aggressive prostate cancer.

Precision Oncology

New knowledge is beginning to explain the decades-old question of why a treatment may work for one patient but not another. Cutting-edge technologies that allow clinicians to identify the mutations present in a patient's tumor cells have resulted in the emerging field of precision medicine, or customized treatments based on the unique biology of an individual's tumor. Precision medicine is an emerging approach to disease treatment and prevention that takes into account individual variability in genes, immune function, environment, and lifestyle for each person.

Doctors now know that each patient doesn't just have prostate cancer, they have their own particular form of prostate cancer.

Someday, the hope is that all treatment will start with a genetic test, followed by custom treatments. Also on the horizon is the concept of "liquid biopsy," where doctors can use blood tests to identify cancer mutations and select treatments.

How can you find out if you are a candidate for a precision therapy? Right now, precision medicine is an emerging field, so many treatments have limited availability, but a good start for anyone with metastatic or resistant prostate cancer is to ask your doctor about precision medicine clinical trials that may be appropriate for you.

Another exciting area of research in prostate cancer relates to the use of immunotherapy. Historically, the problem with curing cancer has been the uncanny ability of cancer cells to reprogram themselves after treatment and hide from the immune system. The promise behind immunotherapy is that for the first time ever, doctors are able to program the body to be smarter than the tumor, and use the immune system to kill the cancer. Numerous ongoing clinical trials are being conducted around the world trying to optimize immunotherapy to treat prostate cancer.



Douglas McNeel, MD, PhD, was one of the earliest researchers to test therapies that activates the body's immune system to fight prostate cancer.

Today, treatments for prostate cancer include many traditional forms of cancer therapy (surgery, radiation, and/or chemotherapy) and some forms that are very specific to the prostate (hormone therapy and precision medicines in clinical trials). Remember that all treatment regimens must be balanced against quality of life concerns, considering the potential side effects of each treatment, the aggressiveness of the cancer, and the overall life expectancy of the patient.

“My cell phone rang. It was the urologist. I stopped what I was doing and got the news. I still remember. He said, “there’s a little bit of cancer.”

— PATIENT



UNDERSTANDING YOUR DIAGNOSIS

No matter the exact words that describe the results of your prostate biopsy, a diagnosis of prostate cancer forever changes everything. It can be confusing, frightening, and overwhelming.

As a newly diagnosed patient, you might be torn by arguments favoring one treatment over another or you may feel ill-equipped to make the decisions that are being required of you. For family members and loved ones, there can be an ache to help and to comfort, but without knowing what a man's needs might be.

DETECTION, DIAGNOSIS AND STAGING

The PSA blood test and Digital Rectal Exam (DRE) can be used to detect prostate cancer when no symptoms are present. They can help catch the disease at an early stage when treatment is thought to be more effective and potentially has fewer side effects.

During a DRE, the physician inserts a gloved, lubricated finger into the rectum and examines the prostate for any irregularities in size, shape, and texture.

During a PSA test, a small amount of blood is drawn from the arm, and the level of PSA, a protein produced by the prostate, is measured. PSA levels under 3.0 ng/mL are usually considered “normal.” However, the assessment of a “normal” PSA must take into account:

- The patient's age
- Prostate size
- Previous PSA tests
- Other medical conditions, such as BPH or prostatitis
- Drugs that may artificially lower PSA, such as finasteride (Proscar or Propecia) or dutasteride (Avodart)
- Infections and procedures involving the urinary tract that can elevate the PSA

Making the Diagnosis via Biopsy

Although a high PSA may increase a doctor's suspicion of prostate cancer, an elevated PSA alone does not confirm a diagnosis of prostate cancer. A PSA test is used to signal whether or not you should have further testing—usually a prostate biopsy—which will determine whether prostate cancer is present. There are 3 main ways men are initially diagnosed:

1. TRUS-guided biopsy: A trans-rectal ultrasound-guided biopsy is the most common way prostate cancer is diagnosed in the US. An ultrasound probe is placed in the rectum to allow visualization of the prostate, then at least 12 needles are placed into the prostate to sample for cancer. If a patient had magnetic resonance imaging (MRI) before the biopsy, needles may be targeted into areas that looked suspicious on the MRI.

2. Trans-perineal biopsy: The prostate can also be biopsied by placing a needle through the skin between the scrotum and anus (perineum).

3. Incidentally: Some men are diagnosed when prostate cancer is found incidentally during an unrelated surgical procedure of the prostate or bladder.

Prostate tissue from the biopsy is then examined under a microscope by a pathologist, to confirm the presence or absence of prostate cancer cells.

Targeted or fusion biopsies are increasingly being utilized at select centers that use an MRI, in addition to the ultrasound, to better visualize tumors within the prostate and help guide biopsy needles. Research on the continued improvement of this technology continues.

PI-RADS (Prostate Imaging Reporting and Data System) is a structured reporting scheme for evaluating the prostate for prostate cancer. The PI-RADS score is assessed on an MRI, for patients who have not yet undergone therapy. The scores are:

- PI-RADS 1: **very low**—clinically significant cancer is highly unlikely to be present
- PI-RADS 2: **low**—clinically significant cancer is unlikely to be present

- ▶ PI-RADS 3: **intermediate**—the chance of clinically significant cancer is neutral
- ▶ PI-RADS 4: **high**—clinically significant cancer is likely to be present
- ▶ PI-RADS 5: **very high**—clinically significant cancer is highly likely to be present

Staging your Disease

There are 4 main components to staging prostate cancer:

- ▶ Your PSA level
- ▶ The grade of your tumor (done via biopsy)
- ▶ The stage of your tumor (termed the T-stage for the prostate tumor)—for example, is the prostate cancer contained completely within the prostate?
- ▶ For some men, getting imaging to determine if the cancer has spread to lymph nodes (termed the “**N**-stage” for **nodes**) or bones or other organs (termed the “**M**-stage” for **metastasis**).

1. PSA: A blood test.

Your doctor should have your most recent PSA tests and, if outdated, they may order a fresh one.

2. Grade: How aggressive the cancer looks.

If prostate cancer is found when looking at biopsied tissue under a microscope, the pathologist assigns a grade to the cancer. There are 2 grading systems currently in use, which can be confusing for patients.

The classical grading system for prostate cancer is called the Gleason score, which ranges from 6 to 10 (6 is low grade, 7 is intermediate grade, and a score of 8 to 10 is high grade).

In 2014, the World Health Organization reorganized the Gleason score with the simpler ISUP (International Society of Urological Pathology) Grade Group system ranging from 1 (low) to 5 (very high).

Many hospitals report both the Gleason score and the ISUP grade group, but there may be hospitals that still only report the old Gleason system.

ISUP Grade Group and Gleason Score Comparison

Risk Group	ISUP Grade Group	Gleason Score
Low	Grade Group 1	Gleason Score ≤6
Intermediate Favorable	Grade Group 2	Gleason Score 7 (3+4)
Intermediate Unfavorable	Grade Group 3	Gleason Score 7 (4+3)
High	Grade Group 4	Gleason Score 8
High	Grade Group 5	Gleason Score 9-10

3. Tumor staging (or T-stage): The extent of the prostate cancer.

The digital rectal exam (DRE) gives information on how extensive the prostate cancer is within the prostate area. In some cases, your doctor may order a prostate MRI to give more information if the cancer extends outside the prostate. Staging is classified as follows:

- ▶ T1: The tumor was found solely by a biopsy done due to an elevated PSA (ie was not detectable by DRE or imaging) or was found incidentally during an unrelated procedure. T1 tumors can be divided into T1a-T1c subcategories, depending on how the tumor was found and its size.
- ▶ T2: The doctor could feel a nodule(s) on your prostate during the rectal exam. T2 tumors can be divided into T2a-T2c subcategories, depending on the tumor location and size.
- ▶ T3: The tumor extends out of the prostate capsule. If the tumor also extends into the seminal vesicles, this is referred to as T3b, if not, it's T3a.
- ▶ T4: The tumor invades into the rectum or bladder (uncommon and advanced).

4. Evaluating for metastatic disease: Has the tumor spread beyond the region around the prostate?

Aggressive cancers (eg PSA >20, ISUP grade group 4 or 5 [Gleason score 8-10], or stage T3-4) usually warrant imaging scans to determine the presence of metastatic disease. Some men whose cancer has less aggressive features may benefit from further imaging and they should discuss this with their doctor. This is most commonly done with a computed tomography (CT) scan and a bone scan. It is important for your doctor to know if your cancer has spread to lymph nodes, bones or other body sites since it will influence their treatment recommendations.

SELECTING YOUR TREATMENT

There is no “one size fits all” approach for precise treatment of prostate cancer.

As a matter of fact, your doctor may not recommend treatment at all (termed observation or watchful waiting), or might recommend putting you under “Active Surveillance” with serial testing and a plan to offer curative treatment for the cancer only if it exhibits signs of progression. It’s important to learn as much as possible about the treatment options available and, in conjunction with your physicians, make a decision about what’s best for you.

Because men diagnosed with localized prostate cancer today may live for many years or decades, it is important to discuss not only cure, but also quality of life.

Your decision-making process will likely include a combination of clinical and psychological factors, including:

- ▶ The need for treatment
- ▶ Your family genetics
- ▶ Your level of risk based on biopsy and exam
- ▶ Your personal circumstances
- ▶ Your desire for a certain therapy based on risks and benefits

FERTILITY OPTIONS

For men who are hoping to father a child in the future, it is vital to have a discussion on fertility preservation and sperm cryopreservation with your physician before you undergo any treatment. You can learn more about these issues in the Side Effects: Fertility section (page 37).

Most men with newly-diagnosed prostate cancer should be seen in consultation with a radiation oncologist and a urologist. For men with more aggressive disease, or metastatic disease, patients should also have a consultation with a medical oncologist. A multidisciplinary prostate cancer care team will give you the most comprehensive assessment of the available treatments and expected outcomes, because each physician has expertise in different areas. Many hospitals and universities have multidisciplinary prostate cancer clinics that can provide a consultation on what team of doctors might be right for you.

In general, for nearly all cases of newly diagnosed localized prostate cancer, the chance of “cure” is now the same whether you have radiation therapy or surgery. In the US the 5-year survival rate for all men newly diagnosed with early stage prostate cancer is greater than 99%. However, one treatment may be preferred for you based on the associated side effects, and your team of doctors will evaluate your type of prostate cancer to develop a treatment plan that may include radiation, surgery, some combination of both, or neither.

The main difference between surgery and radiation therapy relates to quality of life and side effects. Every patient has different priorities in regards to what aspects of quality of life are the most meaningful to them, so it’s important to take time to understand and process your diagnosis as well as the therapy options available to you.

ASSEMBLING YOUR TEAM

Decisions about how to treat your prostate cancer can't be made in a vacuum. A new diagnosis can come with a lot of confusing information and feelings. Many aspects of this disease can affect the way you view yourself, the way you interact with others, and the way others interact with you. Yet at this chaotic time, you'll be asked to make some important decisions, based on your doctors' recommendations. To help you along the way, it's prudent to work with your network of family, friends, and practitioners to align expectations and seek support as appropriate.

Doctors and Practitioners

Where possible, select a physician who specializes not just in cancer but in the nuances of your specific type of prostate cancer. How do you find such a doctor? If you are newly diagnosed, start by consulting your diagnosing doctor, that is, the one who found your prostate cancer. He or she may be an expert in the field, or they may refer you to one or more doctors who are.

Other factors to consider when selecting a doctor:

- ▶ Are they covered by your health insurance?
- ▶ Are they affiliated with a university or research hospital?
- ▶ Does their "bedside manner" align with your personality? Are they analytical? Compassionate? Do they seem interested in making you a partner in this process? Do they seem interested in what is important to you?

Remember:

- ▶ Take your time
- ▶ Don't be afraid to shop around and get second or even third opinions
- ▶ Be careful of random advice, e.g. "surgery is the best" or "radiation is the best" or "eat this herb and your cancer will be cured." For accurate information, use data on reputable websites like pcf.org and those that your doctor recommends.
- ▶ Once you have committed, trust is key, but continue to be your own advocate: ask questions, do research, and remain curious

Doctors and Practitioners Involved in Prostate Cancer Diagnosis and Treatment

Urologists specialize in problems affecting the urinary tract (kidney, bladder, prostate, urethra, penis and related organs).

Urological Oncologists perform surgeries for treating prostate and other urological cancers.

Genitourinary Oncologists perform surgeries for issues of the urinary and genital organs.

Radiation Oncologists specialize in the use of radiation therapy to treat cancer.

Medical Oncologists specialize in treating cancer with medical therapies, such as chemotherapy, hormone therapy, and targeted therapies.

Radiologists or Nuclear Medicine Physicians specialize in interpreting imaging scans that you may have and may also perform specialized biopsies or deliver radioactive medical therapies.

Pathologists specialize in interpreting the results from your biopsy or surgery to determine the type, extent, and grade of your cancer.

Dietitians and Naturopathic Doctors counsel patients on nutrition issues related to cancer and treatment.

Physical Therapists create and execute rehabilitation programs to restore function and prevent disability following treatment.

Occupational Therapists work with patients to help them develop, recover, and improve the skills needed for daily living and working.

Genetic Counselors specialize in understanding and counseling you about inherited risks of cancer for you and your family.

Social Workers, Therapists & Counselors help patients and their families cope with the emotional, social, financial and practical aspects of cancer.

Family

Your family wants to support you. Feelings of powerlessness are a common concern around a cancer diagnosis; your loved ones want—or even need—to do something to feel like they are helping. Normally, this may feel like a fantastic offer. But after a cancer diagnosis, you may feel confused about how much support to accept, request, or reject. Keeping open channels of communication is the key.

Tips for Spouses, Caregivers and Adult Children

- ▶ Agree on how you will make decisions
- ▶ Get ready for changes in routine
- ▶ Understand that there could be emotions from both sides around changes in ability
- ▶ Find out how treatments may affect moods, physical ability, and sexual function
- ▶ It is normal to experience loneliness and fear around a cancer diagnosis. Don't hesitate to seek out a support group for spouses and/or caretakers

Tips for Young Children

- ▶ Keep children informed, as age appropriate, and treat them as part of the team
- ▶ Be realistic but optimistic in your communications
- ▶ For older children, you might encourage them to join a support group. For younger children, consult your therapist for suggestions on how much information to share



“I needed and expected my spouse to be my advocate and help me hear the doctors. I needed my friends to listen and laugh, and not give me platitudes.” – Patient

Your Support Network

Outside of your immediate family, there may be many close friends and colleagues who care deeply about you, and have a strong desire to help. With friends and family who have volunteered their assistance, don't be shy about letting them know a few specific things that would be helpful to you. Examples might include rides to treatment, meals, caring for young children, or performing difficult chores during recovery. And when things feel overwhelming, don't be afraid to reach out for the support of family and friends. On the other hand, don't be shy about saying no to help you don't want, however generous. Many online resources exist for organizing volunteer resources during treatment, such as carecalendar.org or lotsahelpinghands.com.



Work with your network of family, friends, and practitioners to set expectations and seek support where appropriate.

Many friends and family choose to become active in the cancer community in order to diminish the common feeling of powerlessness that can come with a loved one's cancer diagnosis. For more info on getting involved, visit www.pcf.org/take-action.

You

Sadness, fear, sleeplessness, and anger are all normal early emotions around a cancer diagnosis. Coping with these emotions isn't something you should take lightly. Seeking professional help, either from an online community, clergy, a church group, a cancer support group, or a private mental health professional isn't a sign of weakness. Taking care of your mental health is akin to the kind of psychological training that a quarterback goes through to make sure he can keep his head in the game: it's vital. For more information on support resources, check out cancer.org.

PROCESSING YOUR DIAGNOSIS

The final decision on treatment is yours and may be informed by a variety of psychological as well as clinical factors. Sometimes this decision process can be empowering, and sometimes it can be bewildering. For example, although the first instinct may be to choose a therapy from the first provider you see who promises to eradicate the disease, you should take your time to investigate your options. Depending on the features of your cancer, and your age, overall health, and personal family circumstances, Active Surveillance may be the right choice for you. Side effects of each treatment are also important to consider, and only you can know what potential outcomes are acceptable to you. Regardless of which treatment you choose, it's important to observe recommended diet and lifestyle modifications from the moment you are diagnosed.

In the end, after all of your research into different treatment types and side effects, different doctors, and different hospitals, the decision is going to come down to you. If there was one right answer that fit every man, we would tell you! However, the decision is very unique to you and it may not be right for your brother, your friend, or any of the twenty other people you consulted, but you need to decide what is the best choice for you to get started on the road to a better health. Some people find the decision process liberating; others find it beyond their individual ability. Remember that it is okay to feel overwhelmed at first. Use this guide to begin to understand your options, but don't be afraid to rely on professionals, friends, and family to help you navigate your final treatment plan.

Thanks to recent advances in treatment, men who are diagnosed with prostate cancer today have many options available to them. It's important to understand the basics of prostate cancer and identify with your medical team what treatment options are right for you. Here are a few questions to help guide conversations with your treatment providers:

What is my PSA level? If multiple values over time have been collected, how fast has it risen, and what does this mean for me?

What is my prostate cancer grade? What does this mean in terms of our approach to my treatment?

Has my cancer spread beyond the prostate? Can it be cured?

Are there additional tests I can do to gain the most precise understanding of the stage and aggressiveness of my cancer?

Can I avoid treatment at this time and be monitored under something called Active Surveillance? How does it work?

What treatment options exist for this stage of cancer? Which treatment do you think is better for me?

What side effects can I expect from the treatments available to me? Should I worry about impotence, or rectal problems, and are the risks different with different treatments? If I speak to other specialists for second opinions before making a final decision on my plan of action, how do we coordinate it?

What is the effect of the treatments on my fertility? Should I consider sperm-banking or other measures before I undergo any treatments?

Is my cancer likely to come back based on what you know today?

How can I improve the success of my therapy? Are there dietary changes I need to make? What about exercise?

Should I join a clinical trial?

Remember, you want to be a partner in your own care. The more educated and proactive you are, the better. Check in at pcf.org regularly for the latest research news and changes in practice.



“A lot of men are numbers guys. They know their Gleason score down to every biopsy core. I didn’t react that way. For me, it is what it is. Every man is different.”

— PATIENT



CHOOSING A TREATMENT OPTION

A man diagnosed with localized or locally advanced prostate cancer has 3 major treatment options: Active Surveillance, surgery, and radiation therapy. Radiation therapy is sometimes combined with hormone therapy. Surgery is almost never combined with hormonal therapy.

There are other emerging treatment options that patients may consider, which include cryotherapy and high-intensity focused ultrasound (HIFU).

None of these therapies have demonstrated the same long term success as surgery or radiation therapy in clinical trials, and some have shown to be inferior as initial treatment.

As of 2017, HIFU is not approved by the US Food and Drug Administration (FDA) to treat prostate cancer, and is only approved for tissue ablation. This option should be utilized only in the context of a clinical trial. Primary hormonal therapy is not a standard treatment option for men with localized prostate cancer.

Choosing the best treatment for localized or locally advanced prostate cancer is generally based on age, the stage and grade of the cancer, the patient's general health, and an evaluation of the risks and benefits of each therapy option.

RISK GROUPS

Physicians think about localized or locally advanced prostate cancer in terms of “risk groups,” which are assigned before the patient undergoes any treatment. There are 3 general risk groups based on the PSA, DRE, and biopsy, which can further be subdivided to better personalize treatment for each patient.

1. Low risk: Tumor confined to the prostate, the PSA is <10 and grade group 1 (Gleason 6). There is also a subset of extremely “slow-growing” tumors called “very low risk” in which fewer than 3 biopsy tissue samples contain cancer cells and the cancer is not detectable by DRE.

2. Intermediate risk: Tumor is confined to the prostate, the PSA is between 10 and 20, or grade group 2 or 3 (Gleason 7). This category is often divided into a “favorable” and “unfavorable” intermediate risk.

3. High risk: Tumor extends outside the prostate, the PSA >20, or grade group 4 or 5 (Gleason 8 to 10). There is also a subset of very aggressive tumors is called “very high risk” in which the tumor has extended into the seminal vesicles (T3b) or the rectum or bladder (T4), or there are multiple biopsy samples with high grade cancer.

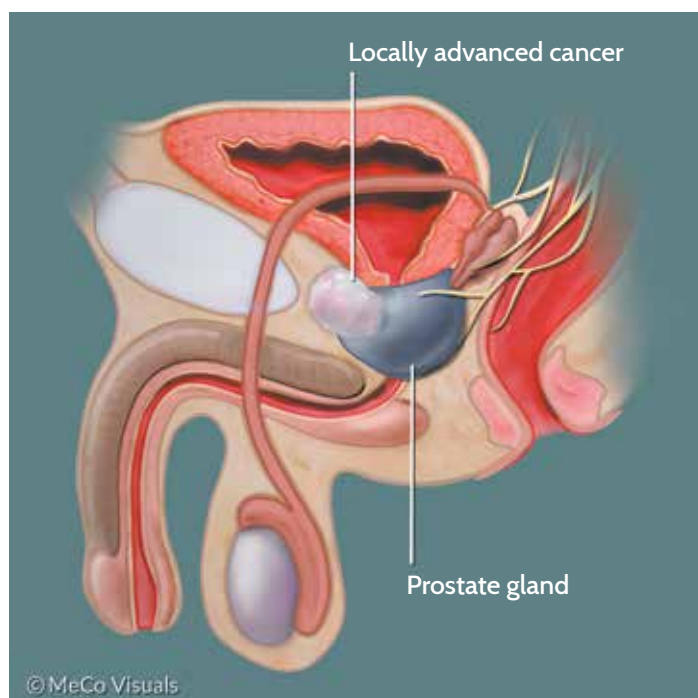
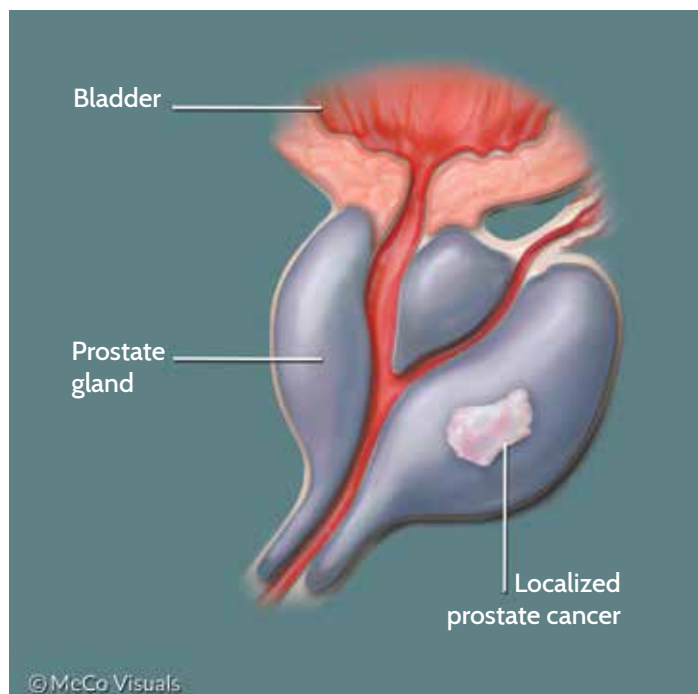
These risk groups are not perfect indicators of your risk for developing recurrent, aggressive prostate cancer. Currently, there are extensive, ongoing efforts to develop tests that can aid physicians in more accurately telling the difference between cancers that will become fatal from those that will sit in the prostate without spreading.

The treatment options for each risk group are very different and you should ask your doctor which risk group you belong to so you can better understand the most appropriate next steps.

How are Risk Groups Determined?

Risk Group	Criteria	Treatments	Notes
Low			
	T1c stage Grade group 1 PSA <10 ng/mL	Active Surveillance or watchful waiting, depending on age	Select patients with higher-volume low-risk disease, strong family history of other cancers, or African American men may be recommended definitive therapy
Intermediate			
Favorable	Any one of the following risk factors: T2b/c stage Grade group 2 PSA 10-20 Also, must have >50% of your biopsy cores negative for cancer	Surgery Radiation therapy	Active Surveillance may be appropriate for select favorable intermediate-risk men Cure rates are equal between surgery and radiation therapy
Unfavorable	Grade group 3 or Can have any two of the following risk factors: T2b/c stage Grade group 2 PSA 10-20 <50% of your biopsy cores negative for cancer	Radiation therapy + short-term hormone therapy Surgery +/- post-operative radiation therapy	Cure rates are equal between surgery and radiation therapy
High			
	Any one of the following risk factors: Grade group 4 or 5 T3 or T4 stage PSA >20	Radiation therapy + long-term hormone therapy Surgery +/- post-operative radiation therapy	New research suggests chemotherapy or abiraterone (known as Zytiga, Abiratas, Abretone, and Abirapro) may improve survival in men with very aggressive localized disease who receive radiation therapy Cure rates appear equal between surgery and radiation therapy

Localized vs. Locally Advanced Prostate Cancer



Localized Prostate Cancer: the cancer has not spread outside the prostate.

Locally Advanced Prostate Cancer: the cancer has spread to nearby organs outside the prostate, but not to distant sites, such as lymph nodes or bones.

ACTIVE SURVEILLANCE

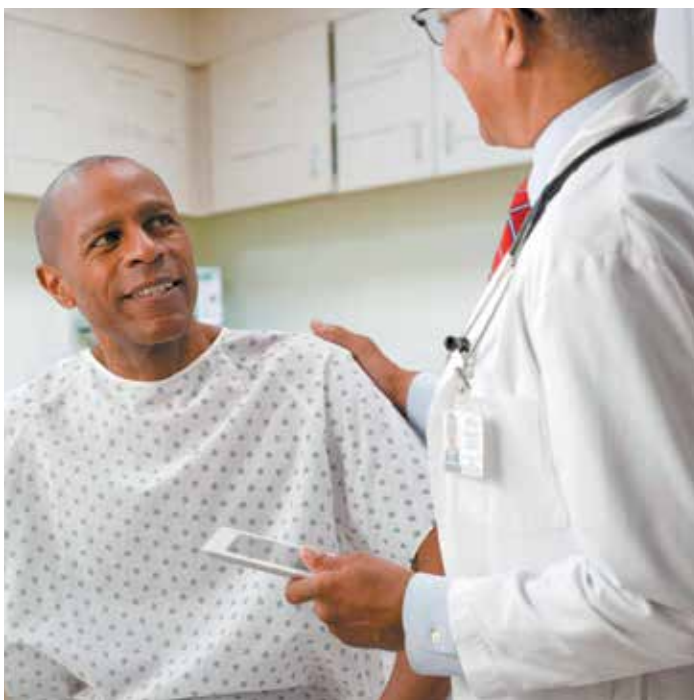
The concept of Active Surveillance has increasingly emerged as a viable option for men who decide not to undergo immediate radical treatment for prostate cancer (surgery or radiation therapy).

Active Surveillance is based on the concept that low-risk prostate cancer is unlikely to harm you or decrease your life expectancy. Over 30% of men have prostate cancers that are so slow growing and “lazy” that Active Surveillance is a better choice than immediate local treatment with surgery or radiation. Of the top 10 most common cancers, prostate cancer is the only one where so many patients have a slow-growing tumor that does not warrant aggressive immediate treatment.

Active Surveillance is not “no treatment,” but rather a strategy to treat you only if and when your cancer warrants treatment (some think of it as deferred treatment only if you need it).

Men with low-risk prostate cancer who have been on Active Surveillance for 10 to 15 years after diagnosis have remarkably low rates of their disease spreading or dying of prostate cancer. In fact, a Johns Hopkins study of men on Active Surveillance found that, 15 years later, less than 1% of men developed metastatic disease. This is important because treatments used for localized prostate cancer—surgery and radiation—have side effects that can alter a person’s quality of life.

The key to these successful numbers is making sure you are monitored regularly for signs of progression. A PSA blood test and digital rectal exam (DRE) are usually done once or twice per year by your urologist, with a repeat biopsy of the prostate every 1 to 5 years. If there is evidence that the cancer is progressing, treatment may be warranted.



Over 30% of men diagnosed with prostate cancer have slow growing or “lazy” tumors that are best monitored with Active Surveillance vs. immediate treatment.

Who Should Choose Active Surveillance?

Some of the characteristics that might qualify you for Active Surveillance include grade group 1, Gleason 6, PSA <10, cancer that is confined to the prostate and/or cancer that is very low volume when biopsied (see page 25 for a full comparison of risk groups).

The ideal candidate for Active Surveillance has low-risk prostate cancer.

The right age for Active Surveillance is a difficult question, as clearly younger men will live longer with their cancers, and thus have a higher likelihood that their cancer could progress. However, younger men who appear to have less aggressive cancers may be able to stay on Active Surveillance longer. Younger

men also have more to lose when it comes to quality of life as they often have better erectile and urinary function than older men.

Active Surveillance may also be more appropriate for men who are currently battling other serious disorders or diseases—such as significant heart disease, long-standing high blood pressure, or poorly controlled diabetes—the patient and his doctors might feel that performing invasive tests or treatment would cause more harm than benefit, except to help manage any symptoms that occur due to advanced disease. There are also select men with favorable intermediate risk who may be good candidates for Active Surveillance.

As with any treatment for prostate cancer, shared decision-making with a physician is necessary. Some physicians also administer commercial genetic tests—such as Decipher, Oncotype Dx® Prostate, and Prolaris®—that may be helpful in determining if you are a good candidate for Active Surveillance.

Active Surveillance is only a good choice for men with sufficient life expectancy to benefit from curative therapy if the cancer were to become more aggressive over time. For older men who have a limited life expectancy, watchful waiting may be more appropriate. Watchful waiting is a more conservative approach without the intent to cure, in which the goal of treatment is simply to manage symptoms as they arise.

SURGERY

Removing the entire prostate gland through surgery, known as a radical prostatectomy, is a common option for men whose cancer has not spread. Other surgical procedures may be performed on men with advanced or recurrent disease, such as removal of lymph nodes, which are initial landing spots for the spread of prostate cancer.

Open radical prostatectomy is the classical way of surgically removing the prostate. In this procedure, the surgeon makes an incision in the lower abdomen in order to remove the prostate. The prostate may also be removed through the perineum, the area between the scrotum and the anus, although this technique is uncommon.

In the last 10 years, **laparoscopic (robotically-assisted) radical prostatectomy** has become very popular. This method requires small incisions to be made in the abdomen. A surgical robot's arms are then inserted into the incisions. With a robotic interface, the surgeon controls the robot's arms, which in turn control cameras and surgical instruments. Some studies suggest a shorter recovery period with robotic compared with open prostatectomy.

Whether open or laparoscopic surgery is chosen, this is a large operation, with a significant healing process. After a 1- to 2-night stay in the hospital, patients typically go home with some form of catheter to help drain urine for 7 to 14 days. In the initial weeks to months after surgery, it is expected and common to have incontinence or leakage of urine, and patients will need to wear adult diapers and/or pads; this generally improves over the first year following surgery. Calisthenics, weight lifting, golf, and many physical activities are prohibited for about the first 2 months after surgery, as the abdominal muscles and urethra heal from the surgery. Physical therapy, including Kegel exercises, can build up pelvic floor muscles and help some patients who are having persistent incontinence. Talk with your urologist about how you can post-operatively increase your exercise tolerance by walking greater and greater distances over the course of your recovery.

POSITIVE MARGINS

After your doctor removes the cancer cells, he or she will examine the cells under the microscope. Your margins are *clear* if no cancer cells are seen at the outer edge of the tissue that was removed. The margins are *positive* if the cancer extends all the way to the edge of the tissue that was removed. Positive margins can imply that some cancer was left behind.

There are 2 other therapies that may be given in conjunction with surgery, based on your pathology report after the surgery:

- ▶ Radiation therapy is recommended in some men with high-risk prostate cancer who have cancer that has penetrated through the prostate capsule (layer of connective tissue around the prostate) and/or who have positive margins after surgery. Research has shown that recurrence rates drop by approximately 50% in men with a positive margin or T3 disease if you add radiation after surgery. You should discuss with your doctor the risks and benefits of radiation therapy following your surgery. Another strategy is to use radiation only if PSA levels rise; this is referred to as salvage radiation. Genomic tests (eg, Decipher, GenomeDx) have been developed that may help you and your doctor decide if you would benefit from adjuvant radiation therapy versus waiting to see if the PSA rises
- ▶ Hormone therapy may be recommended for men who have cancer found in their lymph nodes at the time of surgery; for these men, hormone therapy after surgery has been shown to help patients live longer. Multiple clinical trials have not demonstrated a significant benefit to using hormone therapy before surgery

Keep in mind that new treatment protocols are constantly improving, and you can always discuss with your doctor your eligibility to enroll in a clinical trial for patients who have had a prostatectomy.

COMPARING SURGERY AND RADIATION

In general, for nearly all cases of newly diagnosed localized prostate cancer, the chance of “cure” is the same whether you have radiation therapy or surgery.

The main difference between surgery and radiation therapy relates to quality of life and side effects. Every patient has different priorities in regards to what aspects of quality of life mean most to them, so it's important to take time to understand and process your diagnosis as well as the therapy options available to you.

One treatment may be preferred for you based on the associated side effect profile, and your team of doctors will evaluate your type of prostate cancer and develop a treatment plan that may include radiation without surgery, surgery without radiation, some combination of both, or neither. In some cases, hormonal therapy is added.

RADIATION

Radiation involves the killing of cancer cells with ionizing radiation or photons. Radiation damages the cancer cells' DNA (the genetic material of the cancer cell), leaving them unable to survive, grow, or spread; subsequently, the cancer cells die. Radiation therapy, like surgery, is very effective at killing localized or locally advanced prostate cancer and has the same cure rate as surgery.

Just as surgical skill can play an important role in determining outcomes from prostatectomy, the technical skill of your radiation oncologist can play an important role in radiation outcomes. When choosing a radiation oncologist, at a minimum,

make sure he or she has broad experience with an assortment of approaches and can objectively help you decide on the best course of treatment.

External Beam Radiation Therapy (EBRT)

EBRT is the most common type of radiation therapy. CT scans and MRIs are used to map out the location of the tumor cells, and X-rays are targeted to those areas. There are many types of radiation therapy, each with its own advantages and disadvantages (see inset on the following page).

Regardless of the form of external radiation therapy, it is done on an outpatient basis.

Since it is non-invasive (unlike surgery), there is no down time or healing time. You can be physically active every day of treatment and in the months following. It is common to have mild increased frequency of urination or bowel movements during the weeks of treatment; 2 to 4 weeks after treatment completes, these symptoms generally begin to improve. Many studies have shown that while surgery results in a more immediate loss of erectile function followed by a period of partial recovery, radiation therapy results in a slower loss of erectile function over time in men who had good erectile function before treatment.

In order to receive any of the types of EBRT, you must first undergo what is called a “simulation” or “mapping” scan. This is usually a CT or MRI scan that is used by your radiation oncologist to map the precise anatomy of your prostate, rectum, and bladder so that radiation dosimetrists and physicists can work with sophisticated computer treatment planning systems to design a personalized radiation plan for you.

EBRT Types

3D conformal radiotherapy is a form of radiation therapy that targets the tumor effectively, but also affects a small amount of healthy tissue (such as the rectum or bladder). For this reason 3D conformal radiation therapy is less favored today over more modern techniques that result in very low side effects.

Intensity-modulated radiation therapy (IMRT) uses the power of modern computers and complex computer algorithms to modulate and shape the intensity of the doses and radiation beams in order to better target the radiation delivered to the prostate, while simultaneously delivering lower doses to the bladder and rectal tissue.

Image-guided radiation therapy (IGRT) is a form of IMRT, but even more accurate. IGRT utilizes multiple ways to ensure that the tumor (and not the surrounding tissue) is being treated with high doses of radiation. These methods include placing gold fiducials or electromagnetic beacons that track radiation into the prostate.

Stereotactic body radiation therapy (SBRT) is a form of IGRT. However, what is unique is that treatment is given in just 5 treatments instead of the usual 20 to 44 treatments with classical IMRT/IGRT. SBRT has only been in use for about 10 years for the treatment of prostate cancer, so it is one of the newest forms of radiation therapy and not yet available at all treatment centers. Studies have shown it to be safe and effective, but talk to your doctor for more information. This type of radiation has not been directly compared with the standard radiation to know if it is equally effective.

Proton beam. Protons are similar to photons (X-ray technology). Proton beam therapy has **not** been shown to improve cure rates over other forms of radiation therapy; there are mixed reports of increased and decreased side effects with proton beam. Protons for prostate cancer should largely be viewed as an area of active research, and you should talk to your doctor about them. Insurance companies often do not cover proton beam therapy (unless you are on a research study) and it is typically very expensive.

Treatment Durations

There are 3 common treatment durations, or number of treatments, that are used in EBRT:

- ▶ **Conventional:** For decades, radiation therapy has been delivered every day (Monday through Friday), for a total of 35-45 treatments
- ▶ **Moderate hypofractionation:** Recently, clinical trials that have shown that as few as 20 treatments in 4 weeks can have similar cure rates and side effects as conventional radiation over 8 to 9 weeks. In hypofractionation, the doses given each day are higher than conventional dose levels
- ▶ **Ultra-hypofractionation:** This is essentially SBRT, or treatment delivered in just 5 treatments. These doses are even higher than hypofractionated doses. This strategy is rapidly becoming more common because it has lower side effects, equal cure rates, and increased convenience. However, not all centers provide this treatment, and not all patients are good candidates, so make sure to consult your doctor. This type of radiation has not been directly compared with standard radiation to know if it is equally effective.

Brachytherapy

Brachytherapy involves placing radiation therapy “seeds” or temporary catheters inside the prostate that emit radiation at a very short distance.

Think of it as internal radiation therapy, rather than external radiation therapy. Radioactive seeds (LDR or low dose rate) or catheters (HDR or high dose rate) are inserted directly into the prostate while you are asleep under anesthesia. It is usually done in 1 to 4 treatment sessions depending on the method used. The seeds are permanently placed into your prostate, while the catheters are only temporarily placed inside the prostate and then removed after treatment is done. LDR brachytherapy kills the cancer over many months as the seeds give off radiation to the immediate surrounding area, thus killing the prostate cancer cells. By the end of the year, the radioactive material degrades, and the seeds that remain are harmless.



“I have found a lot of wisdom from other survivors, not just prostate cancer survivors.” – Patient

Brachytherapy by itself is usually used only for low-risk or favorable intermediate-risk patients. It is usually combined with some form of external beam radiation and often hormone therapy for higher-risk patients. The success of brachytherapy, like surgery, is dependent on the skill of your practitioner. Ask your doctor to help you find an experienced radiation oncology team who can perform brachytherapy.

Compared with external radiation therapy, brachytherapy is now much less commonly used, but some patients prefer this option primarily because it doesn't require daily visits to the treatment center. Side effects can include erectile dysfunction, urinary frequency and obstruction, and rectal injury. Patients with large prostates or those patients with a lot of urinary problems are usually poor candidates for brachytherapy. Additionally, patients will need to speak with their doctor regarding restrictions for holding infants in their lap after the procedure.

Hormone Therapy with Radiation

Hormone therapy is often given together with radiation therapy for localized disease (note: it is also used alone or in combination with other treatments for men with metastatic prostate cancer).

Hormone therapy usually consists of a shot that lowers your testosterone, given every 1 to 6 months, depending on the formulation, and sometimes a daily pill that blocks testosterone from reaching the cancer cells. Clinical trials show a benefit in patients who receive hormonal treatment with external beam radiation. Hormone therapy has been shown to improve cure rates of prostate cancer for men receiving radiation therapy and is part of the standard of care for men with certain types of intermediate-risk prostate cancer and nearly all high-risk prostate cancer. It is often given for intermediate-risk cancer for 4 to 6 months (called short-term hormone therapy), and for 2 to 3 years in men with high-risk localized prostate cancer, although some doctors may recommend as little as 18 months of hormone therapy.

Hormone therapy should not be given to men with low-risk prostate cancer and is not a standalone treatment for localized prostate cancer in any risk category.

OTHER THERAPIES FOR LOCALIZED PROSTATE CANCER

Surgery and radiation therapy remain the standard treatment for localized prostate cancer, but other emerging treatment options have recently become available. As time goes on and the benefits of these treatment options are better understood, it's possible that they may be reasonable alternatives for certain patients.

For now, none of these are seen as standard treatment for localized prostate cancer because they lack support from randomized clinical investigations in comparison with radiation or surgery.

Cryotherapy

Cryotherapy, also known as cryosurgery or cryoablation, has been around for years, but is rarely used. With this approach, probes are inserted into the prostate through the perineum (the space between the scrotum and the anus), and argon gas or liquid nitrogen is delivered to the prostate, literally freezing the prostate cells to death.

Over the years, a number of modifications were made to avoid freezing damage to the nearby structures, but the rates for both erectile and urinary dysfunction remain high when it is applied to the entire prostate, and data on long-term outcomes are still limited. There is also investigation into treating only a portion of the prostate with cryotherapy, a type of treatment referred to as “focal therapy.”

Cryotherapy is also used as a secondary local therapy in men who underwent radiation therapy as initial treatment for early-stage prostate cancer. Side effects of this therapy include further urinary or sexual problems such as pain in urination (caused by scar tissue), erectile dysfunction, and urgent need to urinate. Cryotherapy can result in injury to surrounding tissues such as the rectum or bladder given the proximity of these structures to the prostate bed.

“Focal” therapies are treatments that target just a region of the prostate thought to have the tumor, instead of treating the entire prostate gland.

High Intensity Focused Ultrasound (HIFU)

HIFU has been recently approved by the FDA for prostate tissue ablation, but not specifically for prostate cancer. HIFU works exactly the opposite of cryotherapy: with HIFU, the prostate cells are heated to death. A probe is inserted into the rectum, from which very high-intensity ultrasound waves are delivered to the target area. Although this technique remains experimental in the United States, it has been used in Europe for a number of years with some amount of success and failure. Side effects of HIFU are similar to

those discussed above for cryotherapy and depend on the skill and experience of the surgeon using this technique. Using HIFU to treat only the portions of the prostate thought to be cancerous instead of the entire prostate gland (focal therapy) is being investigated.

Primary Hormone Therapy

Since testosterone serves as the main fuel for prostate cancer cell growth, it's a common target for treatment. Hormone therapy, also known as androgen-deprivation therapy or ADT, is designed to stop testosterone from being released or to prevent it from acting on the prostate cells.

Although ADT has always played an important role in men with advanced metastatic prostate cancer, it is also increasingly being used in combination with radiation therapy because studies have shown that this combination increases long term survival.

There is data to show that hormone therapy alone is not an effective treatment strategy for men with localized prostate cancer when compared with radiation. Multiple large studies with very long follow-up have shown that survival is worse with hormone therapy alone compared with hormone therapy with radiation therapy. There are certain rare situations in which the other illnesses that a patient has, a patient's overall health status, or advanced age may make the use of ADT alone a consideration but this is the exception rather than the rule.

“I’m going to do everything I can do at each stage. Nothing heroic. Just whatever I can, I do.”

— PATIENT



IN TREATMENT: WHAT TO EXPECT

Monitoring for Recurrence

After initial treatment for localized or locally-advanced prostate cancer is complete, the next phase in the process is monitoring for a recurrence, or a regrowth of the cancer cells somewhere in your body. Monitoring for recurrence typically involves PSA testing, which is repeated every 6 months for the first 5 years, then yearly from that time on. A prostate exam is typically performed every year as well, but may be omitted if the PSA level is undetectable. If your PSA starts to rise, it could be a sign of your cancer returning, or it could be a sign of something else. The section on What to Do If Your PSA Starts to Rise discusses what men should know about if this happens.

Mental Health

Your psychology, or state of mind has played, and will continue to play, a critical role in your cancer journey. From staying positive to controlling your diet and exercise routine, your overall mental health is a cornerstone in the ongoing treatment and control of your disease.

You may experience new or difficult feelings about your situation. You do not have to face this alone.

Just as with your diagnosis, and regardless of which treatment option you choose, you may experience new or difficult feelings about your situation. This is normal. Living with prostate cancer can affect the way you view yourself and it can affect your interactions with the world around you. As always, it's important to check in with yourself and seek help from your team of doctors, friends and family. Many patients choose to proactively attend support groups with other patients, or begin working with a mental health practitioner. Others feel more comfortable connecting one-on-one with another prostate cancer survivor. Everyone is different in terms of what he needs and how these needs can best be met. The most important thing is to think about yourself carefully and reach out in ways that will work for you. Check with the hospital or cancer center where you received treatment for referrals to counseling services, often free, for patients living with prostate cancer.

Maximizing Quality of Life

As a man with prostate cancer, you may have significant concerns about the side effects of treatment. It is important to communicate with your doctor about your questions and concerns, both when choosing between treatment options, and when undergoing treatment. Find out from your treatment team whether they have recommendations for ways to modify behavior that can reduce or help you avoid specific side effects.

There are many misunderstandings about how often side effects may occur, how severe they really are or should be, and what can be done to manage them and counteract their occurrence. Many of the side effects that men fear most following local treatment are less frequent and severe than they might think. This is due to:

- Technical advances in both surgery and radiation therapy
- Researchers persistently seeking new ways to help overcome side effects
- Improvements in treatment delivery methods

It's still important to understand how and why these effects occur, and to learn how you can minimize their impact on your daily life. It is important to have frank conversations with your doctors about the complications you most want to avoid, and consider treatment options in terms of the likelihood of the risks of these complications.

Is it also of extreme importance that you communicate with your doctors about the side effects that you are experiencing as you undergo treatment. Ongoing and proactive communication will enable your doctor to manage your side effects as early as possible to prevent worsening or development of downstream complications.

Early management of side effects has been shown to help patients live longer, better lives.

POSSIBLE SIDE EFFECTS

Because the prostate is close to several vital structures, prostate cancer and its treatments can disrupt normal urinary, bowel, and sexual functioning.

This section discusses side effects that might be experienced following surgery or radiation therapy for localized or locally advanced prostate cancer. For side effects that may occur with treatments for advanced or metastatic prostate cancer, see Side Effects from Treatments for Advanced Prostate Cancer (page 55).

Urinary Function

Under normal circumstances, the urinary sphincters (bands of muscle at the base of the bladder and at the base of the prostate) remain tightly shut, preventing urine that's stored in the bladder from leaking out. During urination, the sphincters are relaxed and the urine flows from the bladder through the urethra and out of the body.

In **prostatectomy**—the surgical removal of the prostate—the bladder is pulled downward and connected to the urethra at the point where the prostate once sat. If the sphincter at the base of the bladder is damaged during this process, some degree of urinary incontinence or leakage may occur. Nearly all men will have some form of leakage immediately after the surgery, but this will improve over time and with exercises that strengthen the pelvic musculature. Most men regain urinary control within a year, and approximately 1 in 10 men will have some component of mild leakage requiring the use of 1 or more pads per day. This rarely occurs after radiation therapy (about 1 in 100 men). Pelvic floor muscle training with a physical therapist can help. In the case where side effects are severe, an artificial urinary sphincter can be considered.

Radiation therapy is targeted to the prostate, but the bladder is next to the prostate and the urethra runs through the middle of the prostate, so both will receive some radiation. Fortunately these structures are fairly resistant to radiation therapy. However, they can become irritated during and for months after radiation therapy, which usually manifests as a mild increase in urinary frequency and urgency. This can also manifest as nocturia, or waking up more at night to urinate. Nocturia is most common in the few weeks following radiation therapy. These side effects are uncommon after surgery; in fact, for men who have significant symptoms like frequency and nocturia due to prostate enlargement, surgery can actually lead to an improvement in urinary function by simultaneously treating both the prostate cancer and prostate enlargement.

Bowel Function

Solid waste that is excreted from the body moves slowly down the intestines, and, under normal circumstances, the resultant stool exits through the rectum and then anus. Damage to the rectum can result in bowel problems, including rectal bleeding, diarrhea, or urgency.

In **prostatectomy** it is very rare (less than 1%) for men to have altered bowel function after surgery. In rare cases of locally advanced prostate cancer where the cancer invades the rectum, surgery may result in rectal damage.

Radiation therapy is targeted to the prostate, but the rectum sits right behind the prostate. With modern radiation therapy (IMRT or IGRT), it is very rare to have moderate or severe bowel problems. During radiation therapy you may experience softer stools and, rarely, diarrhea (less than 10%). These symptoms typically resolve within a few weeks of completing radiation therapy. With modern radiation, only 2% to 3% of men will have bothersome rectal bleeding that may occur months or years after treatment. Be sure to discuss with your doctor the types of radiation therapy that are appropriate for you, as older forms of radiation therapy (called 3D conformal) can increase rectal side effects significantly.

Overall, it is more common with radiation therapy to have slightly lower rates of overall bowel function compared with surgery. This is temporary and largely resolves by 6 to 12 months post-treatment.

As of 2016, select centers have begun to use an approved device called SpaceOAR, a gel that is injected between the prostate and the rectum in men for whom there is major concern of rectal irritation. It has been shown to further reduce the chance of rectal side effects in some men.

Fertility

After any of the most common prostate cancer treatments—surgery, radiation therapy, or hormone therapy—you are unlikely to be fertile. As part of the surgical removal of the prostate, the seminal vesicles and part of the vas deferens are removed, disrupting the connection to the testes. Orgasm may still occur, but ejaculation will be dry and natural conception will not be possible. Radiation similarly destroys the prostate and seminal vesicles; chemotherapy and hormone therapy are both harmful to sperm production.

If you are hoping to father a child in the future, discuss fertility preservation and sperm cryopreservation with your physician before you undergo any treatment.

Sexual Function

Regardless of whether the nerves were spared during surgery or whether the most precise dose planning was used during radiation therapy, erectile dysfunction remains the most common side effect after treatment. This is because the nerves and blood vessels that control the physical aspect of an erection are incredibly delicate, and any trauma to the area can result in changes. However, even if you do experience some side effects of treatment, there is also room for optimism: many excellent options for managing erectile function (see inset on page 39) exist on the market today.



When choosing a treatment option that is right for you, talk carefully with your doctor about which side effects are most tolerable for your lifestyle.

However, within one year after treatment, most men with intact nerves will see a substantial improvement. The skill of your surgeon or physician can have a significant impact on this outcome, so it's important to select your team carefully. Likewise, men with baseline erectile dysfunction and/or other diseases or disorders that impair their ability to maintain an erection, such as diabetes or vascular problems, will have a more difficult time returning to pre-treatment function. It's important to remember that your functionality after treatment can only be as good as it was before treatment. The best predictor of how you will be after treatment is how healthy you were going into treatment.



Although some erectile function may be lost in some patients during treatment, many options exist for managing side effects (see inset on the following page).

Four main components of erectile function may be affected by prostate cancer treatment:

1. Libido (sex drive) is most commonly affected by hormone therapy, or treatment that decreases your testosterone. You can have a low libido and still obtain an erection, but it is usually more difficult for men who have less interest in sex. This will return once your testosterone returns to normal after completing hormone therapy. Loss of libido can be a major concern for some patients and/or their partner and much less of an issue for others. Couples counseling should be considered if there is a possibility of causing stress in a relationship.

2. Mechanical ability is the ability to achieve a firm erection. It is controlled by the nerves and vessels that are intimately associated with the prostate and structures near the penis. Mechanical ability is most affected by surgery or radiation therapy.

3. Orgasm/climax can be more difficult after treatment, especially if libido is low or your erections are not as firm as they used to be. Also, sometimes there can be some discomfort initially after treatment when you climax. This usually is transient and will resolve. It is important to distinguish orgasm from ejaculation, as men will continue to have the pleasure sensation of orgasm without ejaculation.

4. Ejaculate may be minimal after treatment. The prostate and seminal vesicles which function to produce ejaculate are removed and/or irradiated during treatment, so it is common to have a minimal or no ejaculate afterwards. So although you may be able to have an erection and reach an orgasm, nothing may come out.

Prostatectomy: Since the 1980s, most men are treated with what is termed a “nerve-sparing” prostatectomy. The goal of the procedure is to take the prostate and seminal vesicles out while sparing the nerves adjacent to the prostate. Studies have shown that approximately 50% of men who have the ability to have an erection before surgery will maintain this ability long-term. This number can increase or decrease based on age, obesity, and the ability to spare the nerves. In general, men with lower-risk prostate cancer have higher rates than average of erectile function given it is easier to spare the nerves. In contrast, in men with high-risk prostate cancer it is often more challenging to spare the nerves as the tumor may have spread past the nerves outside the prostate capsule and erectile function rates are lower than average.

Management of Erectile Function

Oral medications such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®), relax the muscles in the penis, allowing blood to rapidly flow in. About 75% of men who undergo nerve-sparing prostatectomy or more precise forms of radiation therapy have reported successfully achieving erections after using these drugs. Consult your doctor to see if these medications might be right for you. Individuals taking medicines that contain nitrates, such as those for angina or heart problems, may not be candidates for these medications.

Alprostadil (MUSE®) is a medicated pellet about half the size of a grain of rice that is inserted into the urethra through the opening at the tip of the penis. Like oral medications, it also stimulates blood flow into the penis. About 40% of men have reported successfully achieving erections after using this drug, but the results are often inconsistent.

Alprostadil (Caverject®) uses the same drug that is in the MUSE pellets, but is delivered via an injection directly into the penis. Although nearly 90% of men using Caverject reported erections about 6 months after therapy, many men have a concern about injecting themselves regularly, so the treatment is often used only after other approaches have not worked.

Mechanical Devices may be a solution for those unwilling or unable to use any form of medication to help improve erectile function, or as an adjunct to medications. The vacuum constriction device, or vacuum pump, creates an erection mechanically, by forcing blood into the penis using a vacuum seal. Because the blood starts to flow back out once the vacuum seal is broken, a rubber ring is rolled onto the base of the penis, constricting it sufficiently so that the blood does not escape. About 80% of men find this device successful, but it, too, has a high drop-out rate. Note that the constriction ring at the base of the penis is effectively cutting off fresh circulation. Because of this effect, it is crucial that the ring be removed immediately after intercourse, or the tissue can be damaged due to lack of flowing oxygen.

A surgically inserted penile implant can be up to 100% effective, and about 70% of men remain satisfied with their implants even after 10 years. The implant consists of a narrow, flexible plastic tube, a small balloon-like structure and a release button. The penis remains flaccid until an erection is desired, at which point the release button is pressed and fluid from the balloon fills the plastic tube, pulling the penis up and creating an erection. Note that the surgical procedure is done under general anesthesia, so this option is not available to men who are not considered good candidates for surgery because of other health reasons.

CONSULT YOUR DOCTOR AS TO WHICH OF THESE OPTIONS MIGHT BE RIGHT FOR YOU.

Radiation therapy: Similar to surgery, damage to blood vessels and nerves after radiation therapy can result in decreased erectile function over time. In general, radiation therapy has less of an impact on erectile function in the first 5 to 10 years after treatment compared with surgery, and approximately 70% of men who have baseline erectile function before treatment will keep erectile function after treatment. However, radiation therapy has a slower delay in erectile function decline than surgery; 15 years after treatment, the rates are similar to those who underwent surgery.

These rates do not appear to be affected in the long-term by the use of short-term (4 to 6 months) hormone therapy, but will be affected by the use of long-term (18 to 36 months) hormone therapy.

Newer techniques in radiation therapy, termed “vessel sparing” radiation therapy, have shown promising results for improving the preservation of erectile function, with close to 80% of men maintaining baseline function. Ask your radiation oncologist about vessel sparing radiation therapy.

PERMANENT UPGRADES TO HEALTHY LIVING

From the moment you are diagnosed with prostate cancer, it's important to make mindful decisions about your diet and lifestyle. Your everyday choices are vital to the success of your treatment and your recovery from the disease, and it's a great way to take back some of the control that cancer and its treatment may have had on your life. Additionally, there is growing scientific evidence that suggests healthy diet and lifestyle practices may actually slow the growth and progression of prostate cancer.

Diet

Just a few simple changes in your daily eating habits can help support healthier living as you recover from prostate cancer, and may even decrease risk of your cancer coming back or getting worse. All of these recommendations also apply to maintaining overall health, for you and your family.

1. Vegetables. Incorporate cooked tomatoes (preferably cooked with olive oil) and cruciferous vegetables (like broccoli and cauliflower) into many of your weekly meals. Certain fruits and vegetables contain large amounts of antioxidants. Antioxidants benefit the body by removing free radicals. Free radicals can attack healthy cells and permanently disrupt their operation.

2. Fat. Try to keep the amount of fat that you get from red meat and dairy products to a minimum. Several studies have reported that saturated fat intake is associated with an increased risk of developing advanced prostate cancer, while long-chain omega-3 fatty acids (the “good fat” found in fish such as salmon) are associated with lower risk. Avoid processed meats (lunchmeats) that contain nitrates, or charred meat, which have been shown to have cancer-promoting properties. Choose fish, lean poultry, or plant-based proteins such as nuts and beans instead.

3. Vitamins. Try to get your vitamins from food sources, that is, eating a diet rich in vegetables and whole grains, rather than relying on vitamin supplements. In particular, avoid calcium substitutes. Rather, get your calcium from low-fat dairy foods and dark green leafy vegetables.

For more detailed information on nutrition, see the Prostate Cancer Foundation Nutrition Guide.

Exercise

Exercise is part of a healthy lifestyle for everyone. For prostate cancer survivors, exercise as much as you are physically able, at a pace which is maximal for your personal fitness.

For those that are able to exercise vigorously, walk as briskly as you can (3+ miles per hour), and try to add bouts of jogging. Vigorous exercise should include close to maximal effort, in which your heart beats rapidly and you are sweating. Such activity includes running, vigorous swimming, or fast bicycling.

Research suggests that exercise affects energy metabolism, inflammation, oxidative stress, immunity, and androgen signaling pathways, and is therefore beneficial for men with prostate cancer. Exercise reduces levels of inflammation. Several studies have shown that vigorous exercise significantly reduced the risk of prostate cancer recurrence, compared with the same volume of exercise at an easy pace.

Lifestyle Changes

In addition to diet and exercise, several other lifestyle factors may be associated with prostate cancer risk and progression.

Smoking

Quitting smoking may reduce the risk of dying from prostate cancer, and reduces the risk of dying from any cause. The health benefits from quitting begin on the first day after smoking ceases. Recent evidence

further suggests that smoking is associated with more aggressive prostate cancer at the time of diagnosis. Furthermore, smokers have a higher risk of prostate cancer progression, including recurrence and metastasis, as well as an increased likelihood of death. Importantly, when compared with current smokers, men who quit smoking more than 10 years ago had prostate cancer mortality risk similar to those who had never smoked.

Body Mass Index (BMI)

Body mass index is a measure of body fat calculated by dividing an individual's weight (in kilograms) by height (in meters squared). A BMI of 18.5 to 24.9 is considered a healthy weight, a BMI of 25 to 29.9 is considered overweight, and a BMI of 30 or higher is considered obese. High BMI is associated with increased risk of developing lethal prostate cancer, and convincing growing evidence suggests that obesity (either before or at the time of diagnosis) is associated with increased risk for prostate cancer recurrence, progression and mortality. This may be due to biological mechanisms that involve insulin, altered levels of male hormones (androgens), and cellular activity in fat tissue. Furthermore, obesity has been shown to increase the rates of urinary incontinence after surgery. Eating a nutritious diet and keeping up your exercise routine will go a long way towards maintaining a healthy weight.



Maintaining a positive attitude along with healthy diet and regular exercise will help during recovery, as well as for the rest of your life.



STOP

The next 2 sections are for men with Advanced Metastatic Prostate Cancer. If you are a newly diagnosed patient with local or locally advanced prostate cancer, we suggest skipping ahead to the section titled “For Our Sons & Daughters,” a discussion of the genetics of prostate cancer risk. Of course, feel free to proceed if you like.

**“Six months after hormone therapy, my
PSA started to rise. That’s when I got
choked up. This was serious.”**

— PATIENT



DETECTING RECURRENCE

At this point, your cancer cells have either been removed with surgery or killed with radiation.

But some prostate cancer cells might have been able to spread outside the treatment areas before they could be removed or killed. At some point these cells may begin to multiply and produce enough PSA that it can again become detectable by lab tests.

If you previously underwent surgery, your PSA should be undetectable; after radiation, there are often residual normal prostate cells that still make some PSA. PSA monitoring after treatment is an important way of understanding whether or not all the prostate cancer cells have been destroyed.

PSA is produced by all prostate cells, not just prostate cancer cells. In order to determine why your PSA is rising, your doctor will first try to determine where the cells producing PSA are located.

This involves imaging, such as a CT, MRI, or bone scan. However, in cases where PSA is still very low, imaging tests may not provide enough information on which to determine a further course of action. So sometimes the next steps are based on the probability (chance) of cure with radiation rather than actually seeing the cancer on scans. Newer molecular imaging scans can be done at select centers; these scans including C11-choline (performed in limited clinic centers), F18-fluciclovine (recently FDA approved), and PSMA PET scans (currently performed only in the context of a clinical trial). These newer scans likewise can have difficulty in finding tumors at low PSA levels.

UNDERSTANDING THE NUMBERS

After prostatectomy, PSA drops to “undetectable levels,” (less than 0.1), depending on the lab performing the PSA test. This is effectively 0, but by definition can never get all the way to zero, given the sensitivity of the test and the fact that, at very low readings, other proteins may be misread as “PSA protein.” In contrast, because normal healthy prostate tissue isn’t always completely killed during radiation therapy, the PSA level rarely drops to 0 with this treatment. Rather, a different low point is seen in each individual, and that low point, or nadir, becomes the benchmark by which to measure a rise in PSA (usually a rise by more than 2.0 ng/mL may be a reason for concern).

Because the starting point is different whether you had surgery or radiation therapy, there are 2 different definitions for disease recurrence as measured by PSA following initial therapy.

Following a prostatectomy, the most widely accepted definition of a recurrence is a confirmed PSA level ≥ 0.2 ng/mL. In the post-radiation therapy setting, the most widely accepted definition is a PSA that is seen to be rising from the lowest level (nadir) by at least 2.0 ng/mL. It’s important to try to always use the same lab for all of your PSA tests because PSA values can fluctuate somewhat from lab to lab.

After radiation therapy, doctors need to look for confirmation from multiple tests because PSA can “bounce” or jump up for a short period, and will later return to its low level. If only one test was performed it’s possible that it could have occurred during a bounce phase, and that the results would therefore be misleading. PSA bounces typically occur between 12 months and 2 years following the end of initial therapy.

WHEN TO BE WORRIED ABOUT RISING PSA

Surgery Patients: PSA greater than 0.2 ng/mL

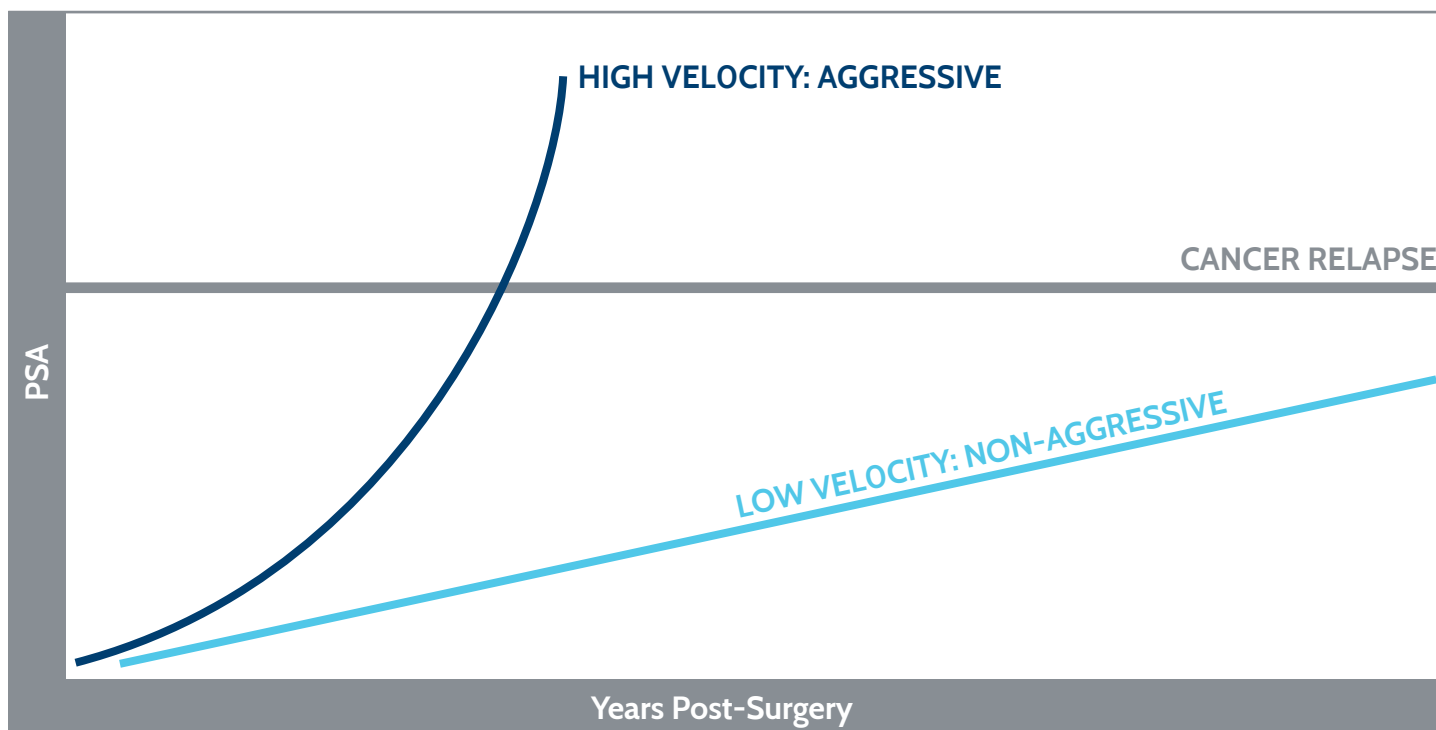
Radiation Patients: if your PSA is 2.0 ng/mL above your lowest reading after treatment (referred to as your “baseline” reading), as measured on 2 consecutive tests

If your PSA is rising but doesn't quite reach these definitions, your doctor might initiate further testing to assess the risk that cancer has come back. This is a gray area that requires a lot of input from your team, possibly including your urologist, radiation oncologist and medical oncologist to help you decide on the best course of treatment.

PSA VELOCITY

The rate (or velocity) at which your PSA rises after prostatectomy or radiation therapy can be a very significant factor in determining how aggressive your cancer is, and can therefore be useful in determining how aggressively it might need to be treated.

PSA Velocity



When looking at PSA velocity in a few hundred men who had undergone either prostatectomy or radiation therapy, researchers found that men whose PSA doubled in under 3 months (fast velocity) had the most aggressive tumors and were more likely to die from their disease, whereas those whose PSA doubled in more than 10 months (slow velocity) had the least aggressive tumors and were less likely to die from their disease.

The faster your PSA rises, the more likely you are to die from your disease.

Measuring and using PSA velocity is an art, not a science. There is no set number of times that your PSA has to be tested in order to determine the rate of rise, although most researchers would agree that more frequent tests over longer periods of time will likely give a better sense of how your tumor is growing.

Ultimately, PSA is just one of many factors that can influence the decision to pursue additional treatments. You and your doctors will need to weigh all of the different factors before deciding on the course that's right for you.

Rising PSA After Initial Treatment

Questions to ask when your PSA is rising after initial treatment.

- ▶ What does it mean that my PSA level is rising?
- ▶ What is my PSA level now and how will we monitor changes over time?
- ▶ Am I a candidate for local “salvage” prostatectomy or radiation? Why or why not?
- ▶ Should I get a CT or bone scan to see if the cancer has spread to my bones?
- ▶ Should we add a medical oncologist to my treatment team to gain an additional perspective on treating my disease?
- ▶ If you recommend that I initiate androgen deprivation therapy (“hormone therapy”), how will this benefit me and slow down the growth of the cancer cells? When is the optimal time to initiate this treatment?
- ▶ What are the benefits and drawbacks/side effects of hormone therapy? Are there things that I can do to minimize the side effects?
- ▶ How long do the treatment effects of hormone therapy last?
- ▶ Should I consider joining a clinical trial?

LOCAL TREATMENTS FOR RECURRENT PROSTATE CANCER

In this section, we'll look at options for what to do when PSA first starts to rise after surgery or radiation therapy, and why a secondary local treatment might be right for you.

In general, the most common site of failure after surgery or radiation therapy is local, meaning in or near the prostate. For this reason, re-treating the prostate region may provide a second chance of cure. However, in some men, PSA may be produced by disease outside the pelvis, such as cancer in distant lymph nodes or bone.

This means that additional local therapy is not right for everyone. It's also important to keep in mind that a second form of local therapy has some degree of additional side effects.

Salvage Radiation Therapy Following Surgery

If your PSA starts to rise after you've undergone prostatectomy, “salvage” radiation therapy might be a good option to explore and is considered part of the standard of care. With this approach, EBRT is delivered to the area immediately surrounding where the prostate used to be (called the prostate bed) and sometimes to the pelvis, with the goal being to eradicate any remaining prostate cancer cells that have been left behind. Approximately 80% of men who have a rising PSA after surgery have disease in the prostate bed.

Note that this procedure is not for everyone. If there are obvious sites of metastatic disease outside of the pelvis, salvage radiation therapy is likely not the best choice, as it will only treat the prostate bed and potentially the nearby lymph nodes.

The side effects that you suffer from salvage radiation therapy are directly related to the amount of side effects suffered from the surgery. In other words, if you had intact urinary control and erectile function after surgery, you are likely to have only mild side effects after radiation therapy. However, if you have some degree of urinary incontinence already or poor erectile function, salvage radiation therapy has the potential to worsen these to a more noticeable degree. In general, salvage radiation therapy (like all salvage therapies) is more likely to cause more side effects than upfront radiation therapy since the side effects may be additive to those previously experienced with surgery. These include rectal bleeding, incontinence (urinary leakage), strictures and difficulty urinating, diarrhea, and fatigue. Be sure to discuss potential side effects with your doctors before deciding on a course of therapy. In some cases, hormone therapy might be given in conjunction with radiation treatment so it is also important to discuss the impact of that with your doctor.

TIMING OF SALVAGE RADIATION

The best time to receive salvage radiation therapy is when your PSA first becomes detectable again, ideally when it is ≤ 0.2 ng/mL, and definitely below 0.5 ng/mL if possible. Once the PSA is above 0.5 ng/mL, cure rates with salvage radiation therapy alone start to fall off quickly. For some men with high risk, hormone therapy is usually added to salvage radiation therapy, which has been shown to improve the cure rate.

Salvage Prostatectomy Following Radiation

In some cases, patients who have residual cancer in the prostate after radiation therapy may have improved results with “salvage” prostatectomy. Much of the data suggest that men who had tumors that were considered potentially curable before radiation (lower likelihood of distant spread at the time of radiation) might do well with post-radiation surgery. But if the tumor had characteristics that suggest it was aggressive, salvage prostatectomy will probably offer little or no benefit.

Even under the best of circumstances, post-radiation surgery is a very difficult operation to perform and can result in significant urinary effects and erectile dysfunction, so few surgeons across the country perform it regularly and successfully. If you talk with your doctors about this treatment approach, be sure to carefully weigh all of the different factors that can play a role in determining whether this approach is right for you.

Brachytherapy Following External Beam Radiation

The use of radioactive seed implantation after EBRT has 5-year disease-free rates of around 50% (very similar to the success of salvage radiation therapy after surgery). Because this approach delivers radiation to very localized areas, it is not an optimal treatment for men with tumors that have spread beyond the prostate.

As with brachytherapy used as a primary therapy, side effects tend to be less frequent and less severe compared with other therapies, such as salvage

prostatectomy. However, some studies have found high rates of urinary incontinence in men undergoing “salvage” brachytherapy, so careful consideration of existing urinary function and expected loss of erectile function should be discussed fully with your doctors before any decision is made.

Cryotherapy Following Radiation

Cryotherapy has been used as a secondary local therapy in men who underwent radiation therapy, and has shown 5-year disease-free rates around 40%. However, because the procedure does not completely destroy all remaining prostate cells, the PSA generally does not drop to 0, so it is often difficult to determine complete success. Men with lower pre-cryotherapy PSA levels and lower grade disease tend to fare better, while those who received hormone therapy in addition to radiation therapy tend to fare worse.

Side effects of cryotherapy tend to be milder compared with standard salvage prostatectomy. Nevertheless, rates for erectile dysfunction and urinary incontinence following this salvage procedure remain high, as do rates for pelvic or rectal pain. Because the severity of side effects tends to correlate with the amount of tissue that is frozen during therapy, better techniques are currently being studied that could improve outcomes over time.

Hormone Therapy Following Radiation

In select men who undergo surgery or radiation therapy, the best salvage treatment option may not be more local therapy, but rather hormonal therapy. This has been shown to be beneficial especially in men who have lymph node involvement that was found at time of surgery. In addition, after radiation therapy, when the PSA is rising but there is no evidence of disease within the prostate via imaging or a repeat biopsy, initiation of hormone therapy alone may be most appropriate at the time when cancer spots are first seen on a scan or with a rapidly rising PSA. See the section on Therapies for Advanced (Metastatic) Prostate Cancer (page 47) for more information on hormone therapy.

THERAPIES FOR ADVANCED (METASTATIC) PROSTATE CANCER

When a man experiences PSA progression after surgery or radiation, primary hormonal therapy is often given at some point, and often for many years. Some men will not require any therapy if their PSA doubling time is quite prolonged and no disease is present on scans.

Advanced disease refers to prostate cancer that has spread beyond the prostate and is unlikely to be cured with surgery or radiation alone.

Men diagnosed with metastatic prostate cancer (their disease has already spread beyond the prostate by the time of diagnosis), will often not undergo local treatments of the primary prostate tumor, such as surgery or radiation. Instead, their therapeutic journey might start with primary hormonal therapy, and from there follow a similar path as men who were diagnosed at an earlier stage and had subsequent disease progression.

Primary Hormone Therapy

Primary hormone therapy (also called androgen deprivation therapy or ADT) is part of the standard of care for advanced metastatic prostate cancer. ADT is designed to stop testosterone from being produced or directly block it from acting on prostate cancer cells. Although hormone therapy is effective at controlling prostate cancer growth, the loss of testosterone has side effects in nearly all men. These side effects range from hot flashes and loss of bone density to mood swings, weight gain, and erectile dysfunction. The timing of when to start primary hormone therapy once the PSA begins to rise is an individual decision and one that should be discussed with your doctor.

For a man starting primary hormonal therapy, doctor visits are usually timed with the hormone therapy injections (which lower your testosterone), along with PSA and other lab checkups such as testosterone levels and liver and kidney function tests.

INTERFERENCE EFFECTS

Many plant-based and complementary medicines can have estrogen-like properties and can interfere with the effectiveness of your hormone therapy, so be sure that your doctor has a complete list of all drugs—including the “non-traditional” ones—that you are taking, so that he or she can better monitor the effects of your therapy on the progression of your disease.

The majority of prostate cancer cells will die or stop growing following the removal of testosterone. However, in many men, some cells gain the ability to grow in the low-testosterone environment created by hormone therapy. As these hormone therapy resistant prostate cancer cells continue to grow, primary hormone therapies have less and less of an effect on the growth of the tumor over time. This state is also referred to as castration resistant prostate cancer (CRPC). Despite this potential pitfall, ADT remains an important step in the process of managing advanced disease, and it will likely be a part of every man's therapeutic regimen if he develops metastatic disease at some point during his fight against recurrent or advanced prostate cancer.

Types of Primary Hormone Therapy (Androgen Deprivation Therapy or ADT)

Orchiectomy: About 90% of testosterone is produced by the testicles. So orchiectomy—the surgical removal of the testicles—is an effective solution to blocking testosterone release. This approach has been used successfully since the 1940s. Because it's permanent and irreversible, most men opt for drug therapy instead. The procedure is typically done on an outpatient basis in the urologist's office. Since recovery tends to be quick and no further hormone therapy is needed, it may be an attractive choice for someone who prefers a low-cost, one-time procedure. It also may have a lower risk of cardiovascular complications and fractures compared with drug-based hormone therapy.



“There’s reason for hope. It’s realistic hope, not pie-in-the-sky hope.” – Patient

LHRH Agonist: LHRH, or luteinizing-hormone releasing hormone, is one of the key hormones released by the body that initiates the production of testosterone (GnRH, or gonadotropin-releasing hormone). Blocking the release of LHRH through the use of agonists (substances that initiate a response) is one of the most common hormone therapies used in men with prostate cancer. Drugs in this class, including leuprolide (Eligard[®], Lupron Depot[®], and Viadur[®]), Goserelin (Zoladex[®]), and triptorelin (Trelstar[®]), are given as regular shots: once a month, once every 3, 4, or 6 months, or once per year. LHRH agonists cause a “testosterone flare” reaction, which is an initial transient rise in testosterone that happens over the first week or two after first treatment. This can result in a variety of symptoms, ranging from bone pain to urinary frequency or difficulty. Fortunately, this can be prevented by co-treatment with anti-androgens.

LHRH Antagonists: These are a newer class of medications that can block LHRH (GnRH) from stimulating testosterone production without causing an initial testosterone surge. This class includes degarelix (Firmagon[®]), which is given monthly to men as an alternative to orchiectomy or LHRH agonists.

Anti-Androgens: Anti-androgens such as bicalutamide (Casodex[®]), Flutamide (Eulexin[®]), and nilutamide (Nilandron[®]) can help block the action of testosterone in prostate cancer cells. They are often added to some hormone injections to prevent a temporary rise in testosterone.

Although the sexual side effects of the anti-androgens when given alone are typically fewer compared with hormone injections, anti-androgens might not be as effective as orchiectomy or hormone injections, and they are not the optimal choice for men with documented metastatic prostate cancer. Furthermore, when given alone, >70% of men experience breast tenderness or the formation/growth of breast tissue, termed gynecomastia.

When used in combination with LHRH agonists, anti-androgens tend to increase the risk of hot flashes, and in rare occasions can result in liver injury. Your liver function should be monitored while you take these medications. Fortunately, gynecomastia is rare when LHRH agonists and anti-androgens are used together.

In addition, nilutamide is known to cause visual light-dark adaptation problems and—rarely—cause inflammation and scarring in the lungs. If you develop a persistent cough or persistent shortness of breath while on nilutamide, you should contact your doctor.

Intermittent Hormonal Therapy

Over the years, researchers have explored different ways to minimize the side effects of testosterone loss while maximizing the therapeutic effect of hormone therapy. The most commonly explored strategy is to give LHRH intermittently, meaning that the drug is taken during “on” periods and skipped during “off” periods.

Intermittent hormonal therapy for the treatment of men with PSA-only relapse (biochemical recurrence or non-metastatic prostate cancer) has been found to be as effective as continuous hormone therapy. It is important to also recognize that it takes a while for testosterone to begin circulating again after LHRH agonists are removed, meaning that ADT injections are effective for weeks and sometimes months before testosterone rises again, and side effects are not immediately reversible.

With intermittent hormone therapy, the LHRH agonist is used for 6 to 12 months, during which time a low PSA level is maintained. If men reach a PSA below a threshold agreed upon by the patient and physician team, hormone therapy can be stopped until the PSA rises to a second agreed upon threshold, at which point the drug is restarted.

During these “drug holidays” when hormone therapy is not being given, some men return to nearly normal levels of testosterone, potentially enabling sexual function and other important quality of life measures to return before the next cycle begins again.

Intermittent therapy has been a very attractive way to limit side effects from hormone therapy for some time. However, at this time, we know that there are limitations to when we can use this approach to treatment, and that only certain men in whom intermittent therapy is appropriate. It is not right for all patients, especially those who have a rising PSA shortly after stopping hormone therapy. A patient-by-patient approach should be used based on degree of response and tolerability to the hormonal therapy.

Combination Treatments for “Hormone-naïve” Prostate Cancer

Abiraterone (Zytiga®) and taxane chemotherapy are 2 therapies that are typically used after cancer becomes resistant to primary hormone therapy (see Therapies for Hormone Resistant Prostate Cancer for more information).

However, several recent clinical trials have found that in men with advanced prostate cancer who are just starting primary hormone therapy (“hormone-naïve”), the addition of abiraterone or taxane chemotherapy significantly extends survival times and length of time before disease progression.

Both of these combinations have similar benefits on cancer outcomes, however, there are different side effects, costs, and other issues that need to be considered with your doctor.

LHRH-Agonists plus Abiraterone

In 2017, results from 2 studies revealed that, in men who are just starting hormone therapy, the addition of abiraterone plus low-dose prednisone to the LHRH agonist Lupron delayed cancer progression by an average of 18 months and reduced the risk of death by 38%, compared with men being treated with Lupron only. Use of abiraterone in this situation has not yet been approved by the FDA, but you can ask your doctor to discuss this approach with you if you are starting hormonal therapy for the first time.

Hormone therapy plus taxane chemotherapy

A recent clinical trial found that the addition of taxane chemotherapy was highly effective in prolonging life for patients starting hormonal therapy for the first time for metastatic disease, who also have a large volume of cancer.

Therapies for Hormone Resistant Prostate Cancer

After a few years, prostate cancer cells often evolve ways to thrive despite the low androgen environment produced by primary hormone therapy, and become “castration-resistant.” For instance, tumors may evolve to produce their own androgens, upregulate the androgen receptor, or acquire mutations in the androgen receptor that allow sufficient activity with little or no androgens. In these cases, because prostate cancer cells still rely on the androgen receptor pathway to survive and grow, a number of “secondary” hormone therapy approaches can be used to keep the tumor from spreading.

TERMS TO KNOW

- ▶ Castration-resistant prostate cancer (CRPC)
- ▶ Hormone-resistant prostate cancer
- ▶ Hormone-refractory prostate cancer

All of these terms refer to the same status: the prostate cancer has learned to adapt and thrive in a low-hormone environment, thus primary hormone therapy is no longer an option and other treatment options should be considered, including second-line hormonal therapies which are even more effective at blocking androgen activity, as well as non-hormonal therapy options and emerging near-term therapies.

For many men who were using an anti-androgen in combination with an LHRH agonist, stopping the anti-androgen, or anti-androgen withdrawal, is the most common first step in secondary hormone therapy. About 10% to 30% of men will respond to anti-androgen withdrawal, which lasts on average 3 to 5 months, during which time additional therapies are not needed. However, inevitably, additional therapies will be needed even if this withdrawal response occurs. Switching to a different anti-androgen might also be able to offer an extra few months of benefit before other therapeutic approaches are required.

Second-line Hormone Therapies

There are 2 major androgen pathway blockers that are used for the treatment of hormone-refractory prostate cancer: **abiraterone** and **enzalutamide (Xtandi®)**. These therapies have exhibited similar survival benefits in similar clinical settings. Therefore, which one is initially prescribed is often driven by its side effect profile combined with other medical issues the patient may have. For example, enzalutamide is preferred if a patient has diabetes to avoid the prednisone that is given alongside abiraterone, and abiraterone is preferred if a patient has memory concerns, seizure disorders, or frailty related to age. Often when there is no medical necessity, insurance coverage and clinical trial options can help inform which agent is used first.

Enzalutamide

Enzalutamide, sold under the brand name Xtandi, is an anti-androgen that acts by blocking the activation of the androgen receptor by testosterone, and is also given orally. Side effects are mild but include fatigue, diarrhea, hot flushes, headache, frailty, falls, memory cloudiness and, very rarely, seizures. Importantly, enzalutamide treatment does not require simultaneous steroid treatment and therefore the steroid side effects can be avoided.

Abiraterone

Abiraterone acetate, sold under the brand name Zytiga, is a pill taken by mouth that blocks the production of testosterone and other androgens, thereby stopping testosterone from stimulating prostate cancer growth. Abiraterone is administered in conjunction with prednisone, a corticosteroid, in order to minimize the adverse effects of abiraterone on other steroid pathways. Although a regimen of abiraterone + prednisone is generally well-tolerated, side effects may include fatigue, high blood pressure, and electrolyte or liver abnormalities and patients need to be monitored regularly.

When treatment with either abiraterone or enzalutamide begins to fail, patients may be switched to the other drug. However, recent studies have indicated that patients who stop responding to abiraterone will have poor responses to enzalutamide and vice versa.

Researchers are actively investigating optimal timing strategies for patients whose cancer has become resistant to enzalutamide or abiraterone—for example, whether the next treatment should be chemotherapy or an investigational therapy.

NON-HORMONAL THERAPY OPTIONS

The therapies described in this section are typically used in patients whose cancer has progressed after treatment with hormonal therapy (ADT). However, clinical trials are continuing to test whether it is useful to introduce each of these treatments even earlier in the course of disease progression.

Taxane Chemotherapy

Currently, taxane chemotherapy, given with prednisone, is the standard of care for men with metastatic prostate cancer that has spread and is progressing despite hormone therapy. Taxane chemotherapy agents approved for the treatment of advanced prostate cancer include docetaxel (Taxotere®) and cabazitaxel (Jevtana®).

Taxane chemotherapy is also effective in prolonging life in patients who have a high burden of cancer on scans when starting hormonal therapy for the first time for metastatic disease.

The decision on when to start chemotherapy is difficult and highly individualized based on several factors:

- ▶ What other treatment options or clinical trials are available
- ▶ How well chemotherapy is likely to be tolerated
- ▶ What prior therapies you have received and how you responded to them
- ▶ If radiation is needed prior to chemotherapy to relieve pain quickly



Although chemotherapy has a historically “bad rap,” prostate cancer chemotherapy drugs can actually help manage pain in metastatic patients.

Often chemotherapy is given before pain starts, with the goal of preventing the cancer from spreading further to other sites. Discuss the use of chemotherapy with your medical oncologist early and often, and keep an open mind despite your concerns about chemotherapy’s “bad rap.” Docetaxel can extend life, reduce pain, and improve quality of life, but it does not cure prostate cancer. For this reason, clinical trials of docetaxel combinations and other promising therapies are a high priority for researchers.

Many men who are suffering from their cancer will experience symptomatic improvement after starting chemotherapy. For example, pain is often reduced in men starting docetaxel, and quality of life is generally better for men with cancer-related symptoms who receive chemotherapy as compared with no therapy.

Platinum Chemotherapy

Platinum-based chemotherapy agents including carboplatin (Paraplatin®), cisplatin (Platinol®), and oxaliplatin (Eloxatin®), are used for the treatment of various cancer types. Platinum chemotherapy is not FDA approved for the treatment of prostate cancer; however, it is sometimes used in very advanced prostate cancer patients who have exhausted all other treatment options or in patients who have rare subtypes of prostate cancer. Patients with advanced disease who are not responding to standard therapy can talk with their doctor about whether they may be candidates for platinum chemotherapy.

Sipuleucel-T Immunotherapy

The immune system has the remarkable ability to kill cells considered dangerous, such as infected cells or cancer cells. However, in most patients with progressing cancer, anti-cancer immune responses either never developed or have been turned off by the cancer. One way to turn on anti-cancer immune responses is the use of therapeutic cancer vaccines, which stimulate the immune system to recognize and fight cancer cells.

Sipuleucel-T (Provenge®) is a cell-based prostate cancer vaccine that has been approved by the FDA for men with metastatic hormone therapy resistant prostate cancer. This treatment is meant for men with minimal or no pain, and is most commonly given before chemotherapy, although it appears to be effective in some men even after chemotherapy.

The treatment process involves filtering out your immune cells, stimulating them in a lab to fight prostate cancer, and then reinfusing those cells back into you intravenously (IV). This process is repeated every 2 weeks for a total of 3 treatments. The goal is to stimulate your own immune system to fight the

cancer cells. This immunotherapy does not lower PSA, treat symptoms, or delay disease progression—however, it has been shown to prolong life. There are ongoing studies attempting to clarify exactly how this treatment works. Sipuleucel-T should only be considered in cases where the patient has a slow-growing tumor and does not need urgent cancer shrinkage (which can be achieved effectively with other agents).

This treatment can only be given in certain centers, and you should discuss with your doctor whether this treatment is appropriate for you.

The side effects of Sipuleucel-T are usually limited to the few days after infusion of the stimulated cells. You can sometimes experience a flu-like illness with fever, chills, nausea, and bone/muscle aches. This generally resolves within 3 days and can be treated with acetaminophen.

Pembrolizumab

Pembrolizumab (Keytruda®) is a type of “immune checkpoint inhibitor,” which are a class of immunotherapies that block immune-suppressive signals and activate tumor-killing immune cells. Pembrolizumab was approved by the FDA in 2017 for the treatment of all solid tumors, including prostate cancer, that have mutations in mismatch repair genes (MMR) and/or exhibit microsatellite instability (MSI) in the tumor. Patients who qualify for this therapy must have progressed on prior treatment and have no satisfactory alternative treatment options. Hence, pembrolizumab would typically be considered after other available effective treatments (such as Sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223, etc.) have been used or deemed inappropriate.

WHAT'S A MMR?

Mismatch repair genes (MMRs) are proteins that work to proofread and edit DNA to prevent mistakes that can lead to mutations and cancer.

Studies suggest that approximately 5%, and perhaps up to 10% of metastatic prostate cancer patients have evidence of MMR mutations and/or MSI in their tumors. Some of these mutations may be inherited, and may be associated with Lynch Syndrome, a condition which predisposes individuals to higher risks of developing certain cancers such as colorectal cancer. At present, regardless of family history, MMR deficiency and MSI are determined by genetic tests performed on biopsies or tumor material from prostate surgery.

Pembrolizumab is delivered intravenously once every 3 weeks. The most common side effects are fatigue, cough, shortness of breath, nausea, constipation, itching, rash, and decreased appetite. Because it works by modifying the immune system, there are rare but serious side effects related to overactive immune responses which are typically treated by stopping the drug and, in some cases, starting steroid medications to suppress the immune reactions.

Radium-223

Radium-223 (Xofigo®) is a calcium-like radioactive element that is used to treat men with hormone-refractory prostate cancer that has metastasized to the bones (but not to other body areas). Because of its calcium-like chemical properties, radium-223 is used in place of calcium to build and fix bones, and is more likely to be taken up in places where the bone has been damaged and is undergoing repair, particularly sites of growing metastases.

Radium-223 has demonstrated both life-prolonging benefits as well as quality-of-life benefits, with more time free of the debilitating complications of advanced prostate cancer (such as bone fractures or spinal cord compression).

It is important to discuss with your doctor the proper sequence of available therapies. Studies have shown that patients with predominantly bone-only metastatic disease do better when radium-223 is given earlier in the course of the disease than when it is given after many lines of therapy (enzalutamide, chemotherapy, abiraterone, etc.), given that it is more likely that patients have cancer spread beyond the bones by this time.

Radiation

Radiation therapy can be used in multiple ways in men with metastatic prostate cancer. The most common reason to receive radiation therapy is to manage pain from prostate cancer spreading to bone. Radiation therapy is very effective at reducing cancer related pain and about 70% to 80% of patients will experience some degree of pain relief after palliative radiation therapy. Usually the radiation therapy is delivered across 1, 5, or 10 treatments. Since this is a pain relief strategy, a low/moderate dose of radiation therapy is used and there are usually very few side effects.

Another indication for radiation therapy is progressive disease within the prostate causing urinary obstruction or bleeding. Radiation therapy is usually given over 1 to 4 weeks in these settings, and is highly dependent on whether you have had previous radiation therapy to the prostate. Less common indications include relieving pain from spine cord compression. EBRT is also used successfully to treat painful bone metastases. This can either be given as a 1-time dose or over 1 to 2 weeks of daily radiation treatments and can significantly improve symptoms. Sometimes radiation therapy may be recommended if there is an area of the bone (typically in the hip or leg) that looks like it may easily break, even if it is not currently painful. The goal in that case is to reduce the risk of developing a fracture. This kind of radiation targeted to sites of painful metastases can usually be safely given, even if you received radiation to treat your initial prostate cancer. More recently SBRT has been used (high dose, ultra-precise radiation therapy, sometimes using only 1 dose).



“My PSA came back high. It was disturbing, but it also was a wake-up call that I had to live my life.” – Patient

Given the many uses of radiation therapy in advanced prostate cancer, talk to your medical oncologist and consult with a radiation oncologist to see if radiation therapy may be an option for you.

Other Bone-Targeting Treatments

When prostate cancer cells spread to the bone, it's known as prostate cancer bone metastasis (as opposed to “primary” bone cancer, which originates in the bones). Bone metastases interfere with the bone's normal health and strength, and if they grow large enough can lead to bone pain, fracture, or other complications that can significantly impair a man's health.

Early detection of bone metastases can help determine the best treatment strategy. It can also help ward off complications. Because men with prostate cancer bone metastases often experience painful episodes, pain management and improving quality of life are important aspects of all treatment strategies.

Treatment with bisphosphonates or denosumab (Xgeva® and Prolia®) can help prevent complications related to bone metastases, like fractures. Bisphosphonates are drugs that are designed to help reset the balance in the bone between bone growth and bone destruction that is disrupted by the prostate cancer metastases.

Zoledronic acid (Zometa®) is a bisphosphonate that can delay the onset of complications associated with prostate cancer bone metastases and relieve pain. It is typically given once every 3 weeks as a 15-minute infusion. Less frequent schedules are sometimes used as well, depending on your individual circumstance and risk.

Denosumab is a different type of bone-targeting drug which is given as an injection, rather than an infusion, and may be used instead of a bisphosphonate.

There are some risks with both classes of bone-targeted agents, including something called osteonecrosis of the jaw, that can occur after deep dental procedures and extractions or sometimes spontaneously. This can result in jaw pain and poor healing of your teeth. Certain laboratory assessments must be monitored with regular use of either medication. Daily calcium and vitamin D supplements are needed, and you should discuss this with your doctor.

Standard Treatment Options for Advanced Prostate Cancer

Disease Stage	Treatments to Consider Once This Stage is Reached
Rising PSA but no detectable tumors on imaging	Hormone therapy Radiation to prostate bed if prior surgery Surveillance
Hormone-naïve metastatic disease	Hormone therapy Hormone therapy + abiraterone Hormone therapy + docetaxel
Metastatic disease; resistant to primary hormone therapy (castration-resistant prostate cancer)	Sipuleucel-T (if minimal symptoms) Abiraterone or enzalutamide Radium-223 (if bone only sites of metastases) Taxane chemotherapy (docetaxel and cabazitaxel)
Patient has exhausted all therapeutic options	Platinum chemotherapy Pembrolizumab (if MMR-deficient or MSI-high) Clinical trials of targeted therapies matched to tumor
Bone protection	Denosumab Zoledronic acid

SIDE EFFECTS FROM TREATMENTS FOR ADVANCED PROSTATE CANCER

This section will discuss the side effects of common therapies used to treat patients with advanced prostate cancer, including hormone therapy and chemotherapy. For a review of side effects from therapies for localized disease, such as surgery and radiation therapy, please refer to Possible Side Effects on page 36. And remember, early management of side effects has been shown to help patients live longer, better lives. Communicate with your doctor as soon as you experience any side effect of treatment.

It is important to understand how and why these side effects occur, so you can minimize their impact on your daily life.

Side Effects of Hormone Therapy

Testosterone is the primary male hormone, and plays an important role in establishing and maintaining typical male characteristics, such as body hair growth, muscle mass, sexual desire, and erectile function, and contributes to a host of other normal physiologic processes in the body. The primary systemic treatment for prostate cancer, ADT, lowers testosterone and causes side effects related to reversing all of the normal functions of testosterone.

Although most men may experience only a few of these symptoms, the list of potential effects of testosterone loss is long: hot flashes, decreased sexual desire, loss of bone density and increased fracture risk (osteoporosis), erectile dysfunction, fatigue, increased risk of diabetes and heart attacks, weight gain, decreased muscle mass, anemia, and memory loss. “Bad” cholesterol levels rise, particularly LDL and total cholesterol, and muscle tends to get replaced by fat, especially around the abdomen.



Reducing red meat and increasing cruciferous vegetables can help during ADT and beyond.

At this time, it is not possible to predict how severely any individual will be affected by lowering testosterone with hormone therapy, but work is being done to find ways to help predict who might be affected by which effects.

Changes in diet and exercise have been shown to relieve many of the side effects of ADT. Before beginning hormone therapy, every man should discuss the effects of testosterone loss with his doctor and nutritionist, so he can alter his lifestyle to accommodate or head off the changes.

Because hormone therapy is part of the treatment of prostate cancer for nearly half of all men with the disease, and is used to treat nearly every man with advanced prostate cancer, it is important to think about ways to prevent, reverse, or identify these effects so that men can live their best lives.

One important approach is considering lifestyle measures that can reduce some of these effects. Eating a heart-healthy diet low in red meat and high in vegetables and fiber, and maintaining physical activity through daily weight bearing exercise can reduce weight gain and maintain bone and muscle mass. Men should also discuss the increased risk of diabetes, heart disease, weight gain, and high cholesterol with their primary care physicians so that they can undergo screening and, if necessary, treatment for these other illnesses throughout the course of treatment for prostate cancer. When making these changes, it is important to talk with a doctor to ensure that you are planning lifestyle modifications that are safe for you. There are also some strategies that can decrease the hot flashes, including medications and acupuncture.

It is important to check bone mineral density around the time of starting hormonal therapy and every 1 or 2 years following, to assess the loss of bone density. There are medications that can be used to reduce the risk of fracture if early signs of bone loss are found.

Side Effects of Chemotherapy

Chemotherapy drugs are powerful and can take a toll on the body. Reactions to drugs can vary widely from patient to patient, so it's important to pay attention to any side effects that you experience, expected or otherwise.

The chemotherapy drug docetaxel is very well tolerated, and many men are surprised to find that disease-related symptoms (pain, fatigue, loss of energy) are improved after starting this therapy. However, docetaxel does have some side effects to be aware of. For example, between 5% and 10% of men will experience a fever with a low white blood cell count that will require medical attention and can be life threatening. The risk can be reduced through the use of white blood cell growth factors (Neulasta®); note that the use of this supportive medication is at the discretion of the physician who must weigh the benefits of Neulasta against its side effects. Despite use of Neulasta, there is still a risk of serious infection. About 50% of men will experience significant fatigue at some point in their therapy, usually for the first week of each cycle. About one-third of men will experience numbness or weakness in their toes or fingers that may interfere with function (neuropathy). This side effect is not always reversible, but in most cases resolves slowly over time. There are no treatments available to prevent neuropathy, but reducing the dose of docetaxel, delaying the next dose, or stopping treatment can slow neuropathy and potentially prevent it from progressing. It is important to talk with your doctor if you are developing neuropathy so that you can speak together about how to best handle further cycles of docetaxel.

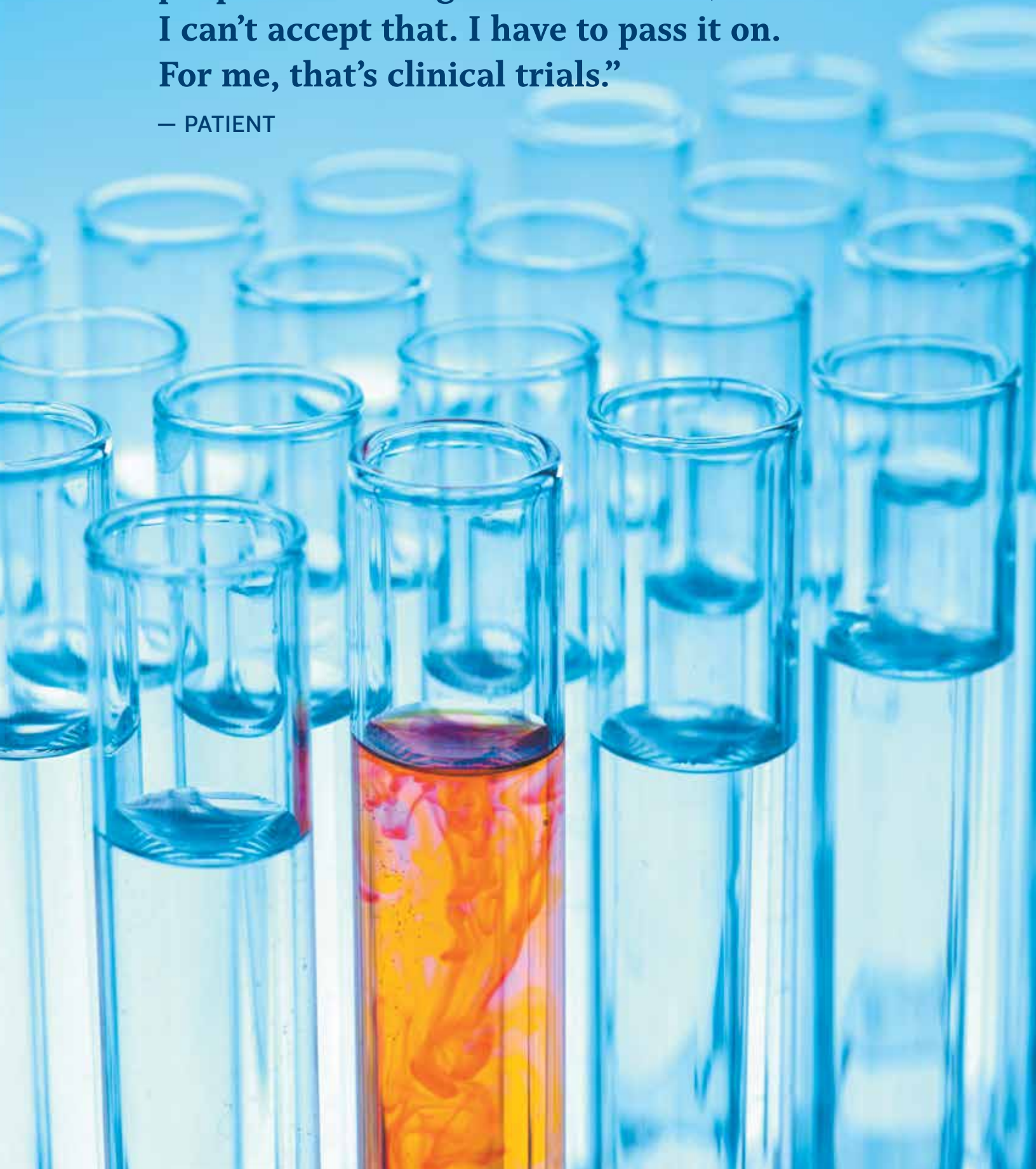
Other side effects of docetaxel include low platelets which can result in bleeding (1%), anemia (5%), reduced heart function (10%), hair loss (65%), diarrhea (32%), nail changes (30%), loss of appetite (20%), shortness of breath (15%), and fluid retention (10% to 20%). Most of these are mild, reversible, and treatable, and should not be a reason to avoid chemotherapy if you need it.

Cabazitaxel, which affects blood counts, is almost always given with Neulasta to boost infection-fighting white blood cells because life-threatening infection due to a depressed immune system is the most serious side effect associated with this medication. A blood transfusion is sometimes necessary to treat anemia to combat the fatigue and shortness of breath related to low blood counts. Other possible side effects include: fatigue (37%), neuropathy (13%), shortness of breath (12%), headache (8%), hair loss (10%), abdominal pain (17%), diarrhea (6%), and low blood pressure (5%). Fortunately, recent data suggests that the side effects of cabazitaxel may be reduced, and the drug equally effective, if it is given at a lower dose than was initially approved. Talk with your doctor about whether the reduced dose of cabazitaxel from the recently reported FIRSTANA trial may be a better option for you than the initially reported and FDA-approved dose.

Regardless of the type of chemotherapy you are receiving, you will be monitored very closely by doctors, nurses, and pharmacists to make sure that all side effects are being addressed. Many of these side effects, especially fever and inability to keep food/drink down, need to be addressed right away—don't wait until your next appointment to tell your provider.

“There’s no way for me to pay back the people who have gotten us this far, and I can’t accept that. I have to pass it on. For me, that’s clinical trials.”

— PATIENT



WHAT IS PRECISION MEDICINE?

Precision medicine uses new diagnostic tests to treat the right patient with the right medicine at the right time based on the genetic make-up of that patient's cancer. The promise of precision medicine is this: someday, there will be no trial and error for prostate cancer drugs. Precision diagnosis is the process of looking at the genetic and molecular characteristics of your unique tumor (uniquely mutated genes and uniquely expressed proteins), and using this information to identify the tumor's weaknesses; think of it like taking your cancer's fingerprint. Because every cancer fingerprint is different, each cancer needs a custom-tailored treatment. Once that level of identification is possible, custom selected treatments have the potential to be effective with no more guess work. Since cancer is a "genomic" disease, that is, most cancers involve mutations of various genes, it makes precision oncology one of the most exciting fields in research today.

Because every cancer fingerprint is different, each cancer needs a custom treatment.

By example, if you have advanced prostate cancer and conventional hormonal therapy is no longer working, you might be helped by a new treatment regime—but you might not. Now, instead of wasting precious time, money and experiencing the side effects of therapies that will not benefit you, you can find out ahead of time if you should take one of these drugs by tests that use either tumor biopsies or your blood to evaluate the genome and molecular make-up of your cancer.

Every day, more and more precision therapies are coming to clinical trials, and hopefully, soon to market. Someday, the hope is that your cancer treatment will be 100% designed for your cancer, and it will be 100% effective. For the latest information on emerging precision therapies, please visit pcf.org.

DID YOU KNOW?

Approximately one-third of metastatic prostate cancer patients have been found to have mutations in genes that repair damaged DNA (known as DDRs or DNA damage repair genes). These mutations have likely contributed to the tumor's development by allowing cells to accumulate more and more mutations, until they become cancer.

EMERGING NEAR-TERM THERAPIES

There are over 1,000 ongoing clinical trials in prostate cancer just in the US that are testing new therapies and therapeutic strategies. Worldwide, there are many more emerging therapies being tested in patients. Only a few of these will lead to practice-changing solutions for prostate cancer patients, including new therapies or improved ways to use therapies that have already been approved. There are however, several emerging therapies that have demonstrated highly promising results in clinical trials for the treatment of prostate cancer and should be noted. Consult your doctor to find out about getting into a clinical trial or to check the status of FDA approval.

PARP Inhibitors

PARP inhibitors, which include olaparib (Lynparza®), rucaparib (Rubraca®), niraparib (Zejula™), and others, are a class of precision medicine treatments that are effective against cancers with mutations in genes that repair damaged DNA. These "DNA damage repair" (DDR) genes including the breast and ovarian cancer risk genes *BRCA1* and *BRCA2*. Approximately one-third of metastatic prostate cancer patients have these mutations in their tumors and may be candidates for treatment with PARP inhibitors.

PARP-inhibitors are not yet FDA approved for the treatment of prostate cancer, but several are now being tested in phase 3 trials (for more information on trial phases see Clinical Trials on page 61). If phase 3 trials

are successful and PARP-inhibitors receive FDA approval, screening of metastatic prostate cancer patients to identify those who have DDR mutations and may benefit from treatment with PARP-inhibitors, will likely become a common practice.

Notably, about 10% of men with metastatic prostate cancer have inherited DDR gene mutations. These patients should have their family members undergo genetic testing and counseling, as inherited DDR mutations increase family risk not only for prostate cancer, but also for breast cancer, ovarian cancer, pancreatic cancer, colon cancer, and others. It is very important to both learn and share with your doctor what cancers have occurred in your other members of your family.

PROSTVAC

PROSTVAC is a vaccine that can help the immune system recognize and target prostate cancer cells. Results from a phase 2 trial testing PROSTVAC in advanced prostate cancer patients demonstrated a median overall survival improvement of 8.5 months. An ongoing phase 3 clinical trial (PROSPECT) is testing PROSTVAC with or without an immune-stimulating agent known as GM-CSF in metastatic hormone-refractory prostate cancer patients with few or no symptoms. Results from this trial are expected in late 2017, but this treatment is not available outside of clinical trials at this time.

THE FUTURE LANDSCAPE OF PROSTATE CANCER PRECISION THERAPY

A few of the most exciting emerging therapies are discussed below, most of which are currently in phase 1 studies.

Precision Medicine

The advent of precision medicine will enable patients to have their tumors profiled for mutations that render them sensitive to certain therapies. Clinical trials are

being conducted to test therapies that target mutations in genes including *PTEN*-loss, *PIK3C*, *AKT*, *RAF*, *WNT*, *CDK*, *IDH1*, *RB*, and others. Investigations into the efficacy of therapies targeting these mutations are only just getting started, and many of these investigational agents will only be offered at select treatment centers—typically academic institutions.

All men with metastatic prostate cancer are now encouraged to speak with their physician about screening to determine whether they may carry one of these inherited mutations.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a class of immunotherapy that activate tumor-killing immune cells. In 2017, the FDA has approved pembrolizumab, prescribed as Keytruda®, a therapy in this class, for patients with solid tumor that have mutations in mismatch repair genes (MMR) and/or exhibit microsatellite instability (MSI). Many studies are underway in prostate cancer to test other checkpoint inhibitors, including pembrolizumab, ipilimumab (Yervoy®), nivolumab (Opdivo®), durvalumab (Imfinzi™), atezolizumab (Tecentriq®), and avelumab (Bavencio®) alone and in combination with various therapies including PARP-inhibitors, cancer vaccines, and radiation therapy.

PSMA Radionuclide Therapy

PSMA radionuclide therapy is a new type of treatment consisting of radioactive molecules injected into your bloodstream that specifically seek out and destroy prostate cancer cells. These agents are available in clinical trials in the US, Australia, and Canada.

CAR T Cells

CAR T cells (“chimeric antigen receptor”) are T cells taken from a patient and genetically engineered to target and kill tumor cells. CAR T cells targeting prostate cancer have begun testing in phase 1 clinical trials in 2017.

CLINICAL TRIALS: HOW TO GET INVOLVED

Finding new treatments, and how to best use new treatments, is the work of clinical trials. As just one example, the first 500 men cured of what was thought to be incurable advanced prostate cancer are expected to be cured on a new clinical trial, even before it is FDA approved.

Clinical trials are the place where patients go to “be there for a cure.”

In clinical trials, researchers test the hypothesis that a certain treatment may be effective for patients, under certain conditions. Clinical trials bring life extending and curative new treatments to cancer patients. Clinical drug trials play a vital role in moving new treatments to patients who need them most, securing data so that FDA approval can be obtained and new drugs can move into widespread clinical practice.

Moreover, for all the promising treatments that have emerged in cancer research in the last several years, there's still a huge task of figuring out exactly the right way to use them. For example, what are the best doses for optimum response? At what time during disease progression and treatment do we insert a drug into the regimen?

There are currently over 120 phase 3 drug trials and more than 650 phase 1 and 2 trials in progress in the US alone. Treatments that are approved will further improve outcomes for patients and join the 8 life-extending drugs that have been approved for men with advanced metastatic prostate cancer:

- ▶ Jevtana® (cabazitaxel)
- ▶ Keytruda® (pembrolizumab)
- ▶ Provenge® (sipuleucel-T)
- ▶ Taxotere® (docetaxel)
- ▶ Xgeva® (denusomab)
- ▶ Xofigo® (radium-223 dichloride)
- ▶ Xtandi® (enzalutamide)
- ▶ Zytiga® (abiraterone)

GET INVOLVED!

Patients who participate in clinical trials become citizen scientists, providing an invaluable service both to treatment science and fellow patients.

For more prostate cancer clinical trial information, visit the Prostate Cancer Clinical Trials Consortium at www.pcctc.org or www.clinicaltrials.gov.

If you are considering a clinical trial, speak to your doctor about the potential benefits of participating in a trial so you can make an informed decision that is best for you.

Remember: A common misconception about clinical trials is that the “placebo” group gets no treatment at all; in fact, they still receive the minimum standard of care.

Clinical Trials

To achieve FDA approval, all new treatments must typically pass through 3 phases of testing.

Phase 1: Test a new agent on healthy volunteer test subjects for overall safety and to find the appropriate dose that can be safely given with acceptable side effects.

Phase 2: Determine if a therapy has any activity against the cancer and can prevent tumor growth, progression, extend a patient's life, or relieve symptoms.

Phase 3: Compare promising treatments from Phase 2 against standard treatments to determine if the test treatment works better and has fewer or more manageable side effects. Phase 3 trials are typically large (hundreds of patients), randomized (each patient is randomly assigned to the standard treatment or the test treatment), and sometimes blinded (the patient and/or doctors are not told which treatment the patient is getting as a way to control for the “placebo effect”).

Phase 4: Approved drugs are continually monitored for safety and efficacy.

“I needed my children to be well and live their lives happily and well, while at the same time being aware of what was going on.”

— PATIENT



THE GENETICS OF RISK

In the last 25 years, several hereditary mutations (genetic mutations that run in families) have been discovered that may increase the risk of developing certain cancers. The most famous that you may have heard of are the *BRCA1* and *BRCA2* mutations that increase risk for breast and ovarian cancer.

Prostate cancer has long been recognized to have a familial component. If you're reading this guide and have received a prostate cancer diagnosis, it's important to speak with your family about risk, prevention, and screening. Having a father or brother with prostate cancer increases a man's risk of developing prostate cancer. The genes that cause this risk have been extensively studied and are complex.

SCREENING FOR PROSTATE CANCER

If you're reading this guide, it's probably because you've already been diagnosed with prostate cancer.

Because we now know so much about the relationship between genetics and risk, it is our hope that readers will immediately consider these issues in consultation with their extended family.

Should My Family Be Screened?

The question of screening is a personal and complex one, which may be further complicated by family history. It's important for each man to talk with his doctor to assess at what age prostate cancer screening might be appropriate.

Revisiting Family Risk

If a family history of prostate cancer or genetic predisposition exists, it is all the more important that your family understand the full picture of risk related to prostate cancer. There are 4 major factors that influence one's risk for developing prostate cancer. Since prevention can hinge on appropriate screening—neither too early, nor too late—it's important to understand your personal risk profile.

Age: The risk of prostate cancer increases with age, and average age at diagnosis of prostate cancer in the United States is 69 years.

Race: African Americans are more likely to develop prostate cancer and have more than twice the risk of dying from it. Conversely, Asian men who live in Asia have the lowest risk; but when they migrate to the west, their risk increases.

Family history: A man with a father or brother who developed prostate cancer has a twofold-increased risk for developing it. This risk is further increased if the cancer was diagnosed at a younger age (less than 55 years of age) or affected 3 or more family members. You should discuss with your doctor if you have a family history of not only prostate cancer, but also breast cancer, ovarian cancer, colon cancer, or pancreatic cancer.

Where you live: The risk of developing prostate cancer for men who live in rural China is 2%, and is 17% for men in the United States. When Chinese men move to the US, their risk increases substantially; men who live north of 40 degrees latitude (north of Philadelphia, Pennsylvania, Columbus, Ohio, and Provo, Utah) have the highest risk for dying from prostate cancer of any men in the United States—this effect may be mediated by inadequate sunlight which reduces vitamin D levels. Similar results were found in Sweden, which is also a high-risk country for prostate cancer: immigrants to Sweden had a lower risk compared with native-born Swedes but, interestingly, the difference diminished the longer they were in Sweden.

While most risk factors are hard or impossible to change. As mentioned, prostate cancer is over 8 times more common in Western culture than in Asia; moreover, when Asian men migrate to western countries the risk of prostate cancer increases over time. Why? Researchers are now looking at prevention strategies which may shed light on this mystery.

There is controversy about the risks and benefits of prostate cancer screening. Benefits include early detection, offering a better chance to cure the disease if your cancer warrants treatment. It also may inform you that you don't need your prostate cancer treated at all.

The problem with screening is that, because most prostate cancers grow very slowly, the side effects of diagnosis (a prostate biopsy) and treatment of low-risk prostate cancers would likely outweigh any benefit that might be gained.

The introduction of PSA screening in the US led to an initial increase in the number of prostate cancer cases diagnoses each year in the USA, but many of these new cases were non-aggressive or low-risk prostate cancer. Very few men will die of these less-aggressive forms of prostate cancer in the first decade after diagnosis.

In 2012 the US Preventative Services Task Force (USPSTF) recommended against the use of PSA screening for healthy men of all ages, stating that the harms of screening outweigh the benefits. In the few years after this recommendation, rates of PSA testing by primary care physicians declined and there was a reduction in the incidence of local and regional prostate cancer.

UPDATED SCREENING RECOMMENDATION

In 2017 the USPSTF issued an updated draft recommendation instead recommending shared decision-making about PSA screening, since the potential benefits and harms of PSA-based screening are closely balanced in men ages 55 to 69 years, and therefore the decision should be an individual one. For men age 70 years and older, they continued to recommend against screening for prostate cancer, with the rationale that potential benefits do not outweigh the harms.

BEGIN SCREENING AT AGE

40	▶ If you have a family history
45	▶ If you are African American
50	▶ If you have no history and you are not African American
55-69	▶ Discuss with your doctor
Over 70	▶ Screening not recommended

Other professional organizations, such as the American Society of Clinical Oncology and the American Urological Association, also recommend shared decision making about PSA screening. They maintain that PSA screening should be considered in the context of a man's life expectancy, family history, ethnicity, and other medical conditions. Experts agree that there is no role for PSA screening for men expected to live less than 10 years, since the rigor of some treatments and side effects can actually lessen life expectancy as well as quality of life. Ultimately, it's recommended that you practice precision screening, and consult with your doctor to come up with a screening plan that's right for you.

When to Start—and Stop—Screening

Age 40 is a reasonable time to start screening for those at highest risk (genetic predispositions or strong family histories of prostate, breast, or ovarian cancer at a young age).

When to start screening is generally based on individual risk.

For otherwise healthy men at high risk (positive family history or African American men), starting at age 40 to 45 years is reasonable. For average-risk men, screening is typically recommended starting at age 50. For men ages 55 to 69 years, guidelines currently recommend shared decision making with the physician about screening. In general, all men should consult with their doctor and create a proactive prostate health plan that is right for them based on their lifestyle and family history.

When to stop screening is also controversial. Some groups propose 70 to 75 years of age as a reasonable cut-off age. Other groups suggest this is an individual decision based on life expectancy and overall current health. There is general agreement that men with a life expectancy less than 10 years have more harm than benefit from prostate cancer screening.

For more info on the latest US Preventative Services Task Force recommendations visit www.pcf.org/uspstf-faqs/

Screening and Biopsy

PSA screening may reveal results that prompt a doctor to recommend a biopsy. However, the result may create more confusion if the PSA is mildly elevated. Fortunately, there are many other supplementary tests and considerations that can help a man who is undergoing screening to decide if a biopsy is necessary, including:

- ▶ Free PSA test (<25% Free PSA indicates greater risk of having cancer)
- ▶ PSA velocity or the rate of rise over time (faster increases means more risk)
- ▶ PSA density, or the PSA per volume of prostate (higher density means more risk)
- ▶ Digital rectal exam results
- ▶ PSA-based markers (for instance the prostate health index, 4K score)
- ▶ Other markers, a urinary PCA3 test
- ▶ MRI of the prostate

It should be noted that these recommendations apply only to screening—testing of healthy men without symptoms. Once the diagnosis of prostate cancer is confirmed by biopsy, PSA is still used for monitoring the status of the cancer, and the interpretation of results depends on how the cancer is managed. Discuss these individual tests with your doctor to make screening decisions that are best for you.



We now know: some of the same genes that are responsible for prostate cancer are also responsible for cancers in daughters.

PROSTATE CANCER GENES IN FAMILIES

For most patients, it is thought that multiple genes together lead to the highest risk. However, we have recently learned that there are certain relatively rare genes that run in some families and when present, may increase a man's risk of developing prostate cancer; in some cases, these genes lead to the more aggressive forms of prostate cancer. In 2016, a PCF-supported study of men with metastatic prostate cancer found that >10% have inherited cancer risk genes such as *BRCA1*, *BRCA2* and 15 other newly-discovered genes that may be important to risk of prostate cancer and other types of cancer.

17 different genes have been identified that run in families with prostate cancer (hereditary prostate cancer).

This is important because it highlights that men should be aware of their family history of cancer—not just prostate cancer, but also breast, ovary, pancreas, leukemia, and other cancers.

Having a sister with breast cancer diagnosed at an early age (in her 40s or younger) may be valuable information for a man to know and share with their doctor.

Do You Carry A Genetic Mutation?

All men with metastatic prostate cancer are now encouraged to speak with their physician about screening to determine whether they may carry one of these inherited mutations. Talk to your doctor about a referral to a genetic counselor if you have any of the following risk factors that may indicate the presence of a hereditary cancer-risk mutation:

- ▶ Personal history of metastatic prostate cancer
- ▶ Blood relative with a known cancer risk gene (eg, *BRCA1*, *BRCA2*, Lynch syndrome, etc)
- ▶ Two or more family members with prostate cancer at Gleason ≥ 7
- ▶ One male relative with metastatic prostate cancer and/or who died from prostate cancer
- ▶ Three or more family members, on the same side of the family, with one or more of the following cancers: breast cancer diagnosed at <50 years old, ovarian cancer, pancreatic cancer, colon cancer, other cancers

“CASCADE” GENETIC TESTING

Different from standard PSA screening for prostate cancer, cascade genetic testing is a form of screening that identifies whether family members share a genetic mutation. For example, if a man discovers that he is a carrier of a hereditary mutation in the *BRCA1*, *BRCA2*, or other genes that increase risk for prostate cancer, this has critical implications for all his family members. Not only will male family members who have inherited

the same mutations be at increased risk for prostate cancer and other cancers such as breast and pancreatic cancer, but female family members who have inherited these mutations may be at increased risk for pancreatic, breast, ovarian, and endometrial cancer. These mutations may also increase risk for pancreatic and other gastrointestinal cancers.

Men who find they are gene mutation carriers should encourage “cascade” (i.e. setting off a cascade of events) genetic counseling and testing for male and female family members, to assess whether they, too, are carriers of the mutation and are at risk for certain cancers.

Family members who learn that they are carriers need to discuss their findings with genetic counselors and their doctors to determine their risk and recourse for various cancers.

Certain gene mutations may have enough information known about them to recommend more frequent screening for specific cancers in family members. Other gene mutations may have less known about them and/or tests can result in variants of uncertain significance. These may require further discussion with a genetic counselor and patients/families with these may consider participating in research registries to help doctors and researchers learn more about those specific variants.

For some genes which are better studied, there may be clear screening recommendations and risk-reduction strategies, such as medications and/or preventative surgeries for women at increased risk for breast and ovarian cancers. However, these decisions must be made with a well-informed genetic counselor and physician. While this information can have important benefits, it can also cause unnecessary worry and/or medical

procedures if the family members or doctors are not fully informed. Early detection and management of cancer risk is a very specialized field and it is strongly recommended that families consider consulting doctors at a Center of Excellence (a medical center actively engaged in the latest research and treatments) to get the most updated information, recommendations and the best medical plan if they are found to have a cancer risk mutation.

THE NUANCES OF GENETIC SCREENING

Many genetic testing companies are offering services to find hereditary mutations in cancer-associated genes. It is critical to be aware that the risk for any given cancer that is associated with any given mutation is not always clear. There are several well-studied mutations that researchers believe are more often present in patients with cancer. However, there are many more mutations that are less well studied, but have been observed in cancer patients, and therefore have some association with risk that is not yet well understood. Importantly, there are many more mutations of “unknown significance,” that have not been previously observed, and though “mutated,” we do not know whether they confer a change in the gene that is sufficient to increase cancer risk.

How To Get Genetic Counseling and Testing

If you or someone in your family has been treated for prostate cancer, your family’s urologist or oncologist may have a recommendation for a local genetic counselor and testing center.

You can also find a list at the National Society for Genetic Counselors: www.nsgc.org



Fish, berries, cooked tomatoes, broccoli, and green tea are five of the top foods for protecting your prostate.

PREVENTION

The ultimate goal is to prevent men from ever developing prostate cancer. Although significant progress has been made, the evidence is not strong enough to form conclusive recommendations on how to prevent prostate cancer. Note that screening does not lead to prevention, but only to earlier detection.

Improvements in diet and exercise are among the most commonly accepted strategies for prevention. This remains an active area of investigation with numerous ongoing studies examining the impact of medications, supplements, diet and exercise on prostate cancer risk.

As a critical prevention strategy, it is important to share these diet and exercise tips with family members who may be at risk.

DIET AND EXERCISE

For those with a family history of prostate cancer, it's important to make some preemptive, permanent lifestyle changes to maintain the best possible health (see inset on the right).

Beyond genetics, diet and exercise are believed to be 2 of the major risk factors for prostate cancer. There is much hope on the horizon for men with prostate cancer and their families. Continuing to be prudent to risk factors, screening recommendations, and diet and exercise changes can help men with prostate cancer live longer and better lives.

In closing, although living a healthy lifestyle and eating right are good for you, they will not eliminate your risk of prostate cancer, nor will they cure you by themselves if you are diagnosed with prostate cancer. If you are age 50 or over, if you are age 40 or over and African American or have a family history of prostate cancer, regular exercise and a good diet are even more critical for reducing risk; consider regular rectal examinations and PSA tests, and discuss the risks and benefits of these screening procedures with your doctor.

Remember: Every patient is unique. Be sure to take these general guidelines and discuss all available options, information, and questions with your physician.

Lifestyle Changes for Prostate Cancer Prevention

1. Adopt an “anti-inflammatory diet”: Eat fewer calories AND exercise more so that you maintain a healthy weight.
2. Try to keep the amount of fat you get from red meat and dairy products to a minimum.
3. Watch your calcium intake. Do not take supplemental doses far above the recommended daily allowance. Some calcium is okay, but avoid taking more than 1200 mg of calcium a day.
4. Eat more fish—evidence from several studies suggest that fish can help protect against prostate cancer because they have “good fat” particularly omega-3 fatty acids. Avoid trans fatty acids (for example, margarine, microwave popcorn, packed baked goods).
5. Try to incorporate cooked tomatoes that are cooked with olive oil and cruciferous vegetables (like broccoli and cauliflower) into many of your weekly meals. Soy and green tea are also potential dietary components that may be helpful.
6. Avoid smoking for many reasons.
7. Drink alcohol in moderation, if at all.
8. Drink coffee. Wait, is that a typo? Nope. Recent studies have shown that drinking unfiltered “Italian style” coffee can lower your risk for prostate cancer.
9. Seek medical treatment for stress, high blood pressure, diabetes, high cholesterol, and depression. Treating these conditions may save your life and will improve your survivorship with prostate cancer.
10. What about supplements? Avoid over-supplementation with vitamins. Too many vitamins may “fuel the cancer,” and while a multivitamin is not likely to be harmful, if you follow a healthy diet with lots of fruits, vegetables, whole grains, fish, and healthy oils you likely do not even need a multivitamin. Ask your doctor about herbal supplements as some may harm you.
11. Relax and enjoy life. Reducing stress in the workplace and home will improve your survivorship and lead to a longer, happier life.





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