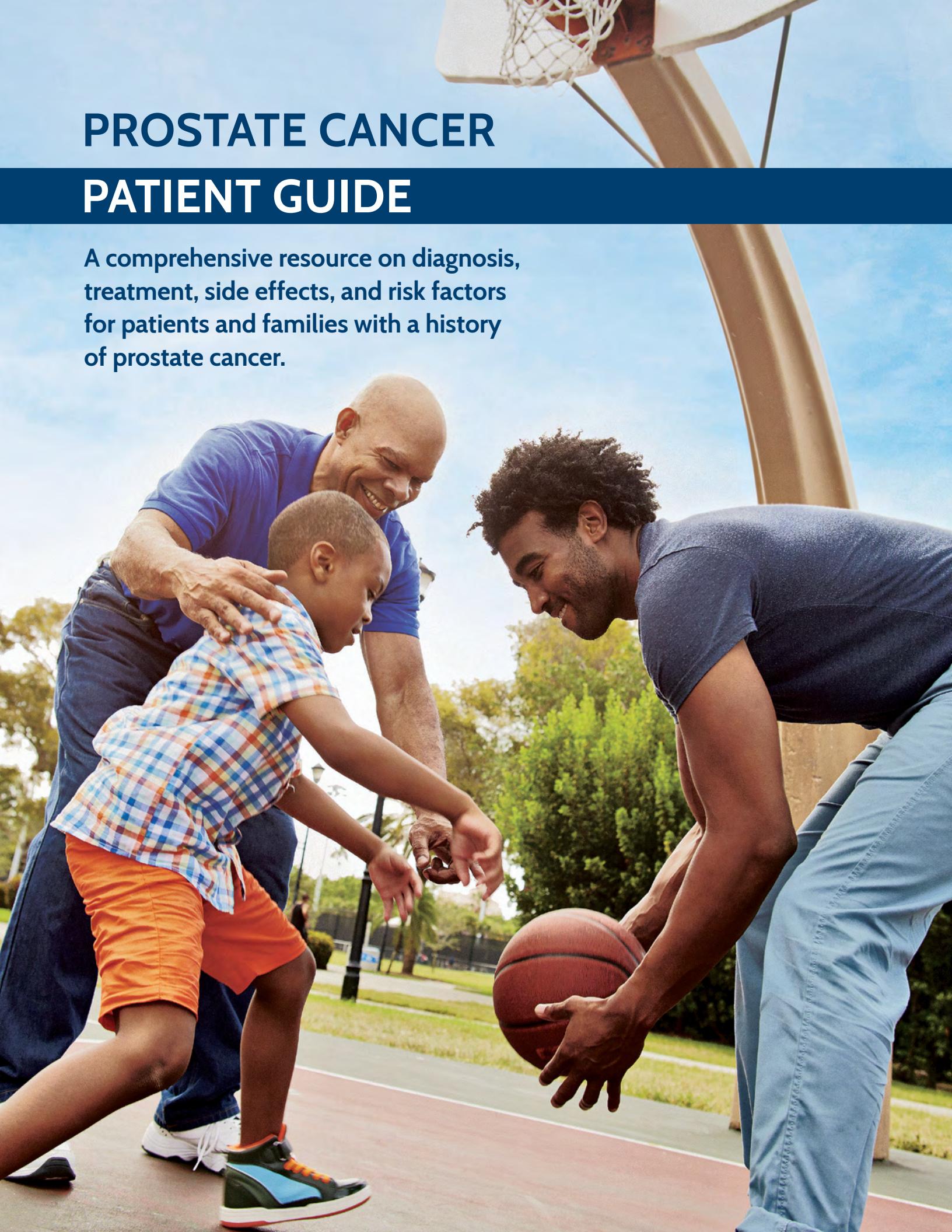


PROSTATE CANCER

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: being 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 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 third edition of the guide focuses all of the most current and most accurate 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 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 shared genes affect their own short- and long-term risk factors—and when they should be screened.

We gratefully acknowledge the scholarly expertise and contributions of our editors, who are world leaders in prostate cancer research: Daniel Spratt, MD (Case Western Reserve University); Heather Cheng, MD, PhD (University of Washington, Fred Hutchinson Cancer Research Center); Stacy Loeb, MD, MSc, PhD (hon) (New York University and Manhattan Veterans Affairs); Alicia Morgans, MD, MPH (Northwestern University); Matthew Cooperberg, MD, MPH, (University of California San Francisco); Wassim Abida, MD, PhD (Memorial Sloan Kettering Cancer Center); Arthur Burnett, MD, MBA (Johns Hopkins University); Nima Sharifi, MD (Cleveland Clinic); William Aronson, MD (UCLA); Angelo Baccala Jr., MD, FACS, MBA (Lehigh Valley Health Network); Neal Shore, MD, FACS (Carolina Urologic Research Center); James Schraadt (Us TOO); Andrew Armstrong, MD (Duke University); Bill Curry; Izak Faiena, MD (Columbia University and James J. Peters VA Medical Center); Christopher Sweeney, MBBS (Dana-Farber Cancer Institute, Harvard Medical School); Howard Soule, PhD (Prostate Cancer Foundation); Stuart Holden, MD (Prostate Cancer Foundation); Jonathan Simons, MD (Prostate Cancer Foundation); Andrea Miyahira, PhD (Prostate Cancer Foundation); Julie DiBiase, PhD, MFA (Prostate Cancer Foundation); and Rebecca Campbell, MD, MPH (Prostate Cancer Foundation).

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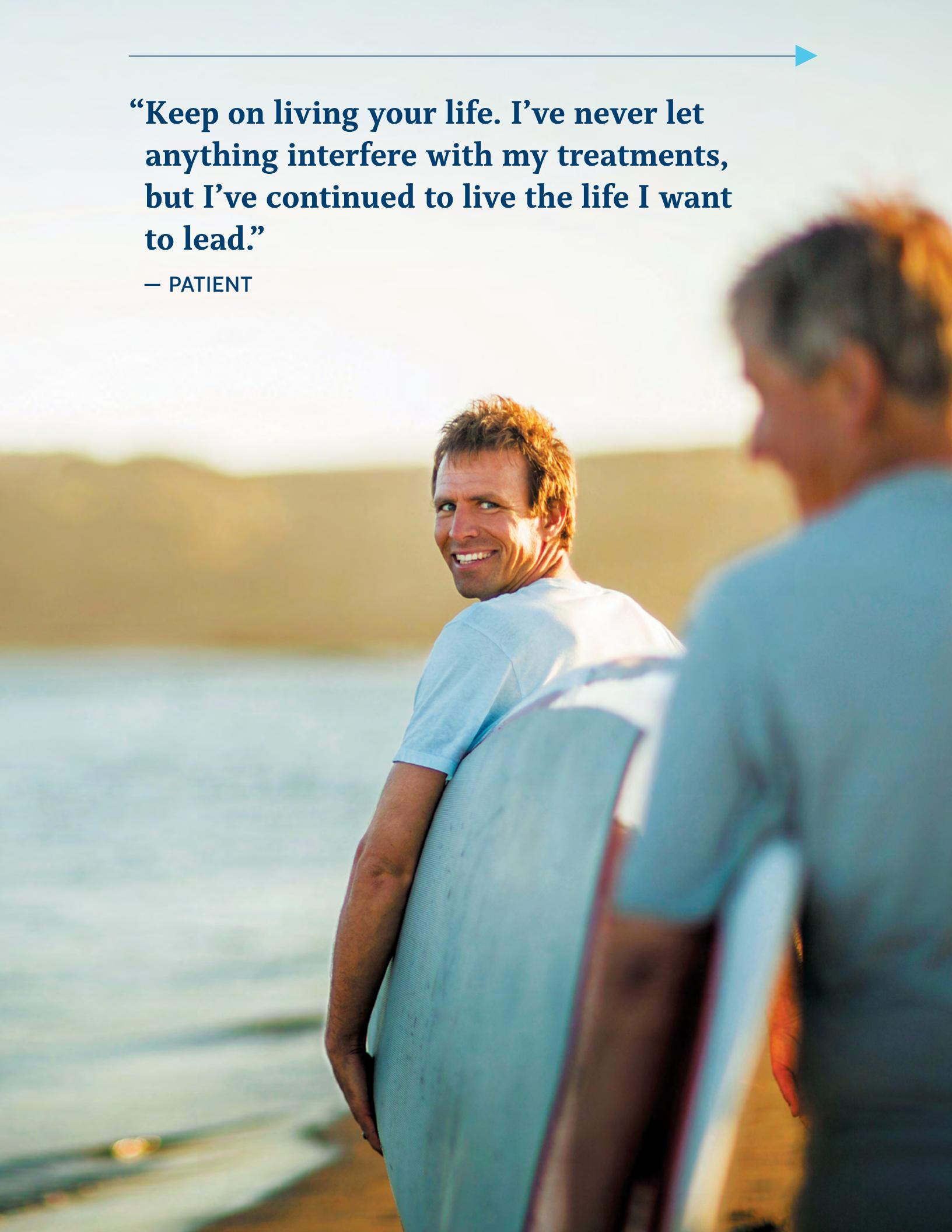
Subjects depicted are models and are used for illustrative purposes only. Prostate cancer standards of practice change regularly. For the most up-to-date information, please register for updates at pcf.org/updates.

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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. The **prostate** is 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

Nearly 90% of all prostate cancers are detected when the cancer is in the prostate or the region around it, so treatment success rates are high compared to most other types of cancer in the body. **The 5-year relative survival rate in the United States for men diagnosed with local or regional prostate cancer is greater than 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 prostate cancer can be aggressive even when it appears to be confined to the prostate.

Even though there is 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. It is the second leading cause of cancer death among men in the U.S., with an average of 94 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. Many men with “low-risk” tumors can safely undergo active surveillance, in which they are monitored without immediate treatment (and treatment-related side effects). In most cases, the key to survival is early detection.

Rates of Diagnosis

Prostate cancer is the second most-diagnosed type of cancer in men. More than 268,000 new cases are estimated in the U.S. for 2022, and about 1.4 million men were diagnosed globally in 2020. Approximately one in eight men in the U.S. 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 456 men under age 50 will be diagnosed, the rate shoots up to 1 in 54 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.” Thanks to advances in treatment in the last 15 years, it is often possible to say that a man has been “cured” of prostate cancer. However, more often, doctors and 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 rare cases, prostate cancers can recur even 15 years after treatment. So instead of using the term “cure,” doctors commonly use terms such as *biochemical control* (PSA levels kept at bay or PSA undetectable) or *in remission* (no cancer can be detected) to help quantify the success of prostate cancer treatment.

20 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.



Prostate cancer can be silent — it's important to get checked, even if you have no symptoms.

99%

Prostate cancer is 99% treatable if detected early.

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

10 THINGS TO KNOW

Black men are about 75% more likely to develop prostate cancer.

75%

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



Thanks to emerging science, we may achieve the goal of ending all incurable prostate cancer.

In the U.S., prostate cancer is the **most common** non-skin cancer in men.

2X

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

Prostate cancer is almost always 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 89).

Risk Factors

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

Genes that increase risk for cancer can run in families. Genetic factors contribute to more than half (57%) of all prostate cancers, which makes prostate cancer the most “inheritable” of all cancers. Men who have a close relative with prostate cancer may be 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, ovarian, colon, or pancreatic cancer.

There are also some individual genes that we now know increase the risk of prostate cancer, and men with these genes may need to undergo genetic counseling, be screened differently, or consider changes in treatment. For more on family risk, see [The Genetics of Risk](#), page 89.

Researchers are still working to understand the complicated reasons why Black men are about 75% more likely to develop prostate cancer compared with white men, and over 2 times more likely to die from the disease.

Prostate cancer appears to develop about 3 years earlier among Black men, on average, than among white men. How this phenomenon relates to environmental factors—such as diet, stress, and exercise; socioeconomic factors—such as those related to access to healthcare; or genetic factors—such as genes that run in families, remains unclear.

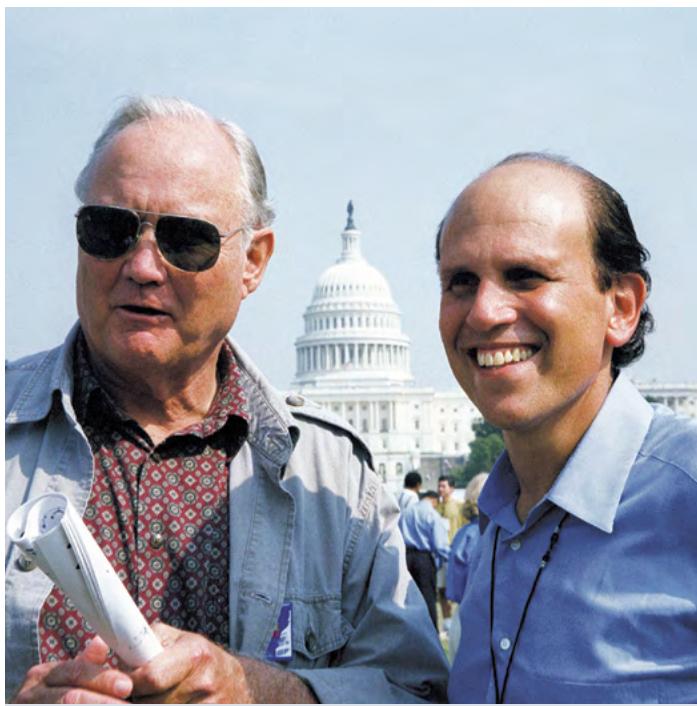
Inherited cancer risk and treatment are active areas of research for the Prostate Cancer Foundation. In the meantime, it is important to keep in mind that not every Black man will get prostate cancer, and that all prostate cancer has a better chance of being managed and cured if it is detected early.

Other risk factors for prostate cancer diagnosis and negative outcomes are [social and environmental factors](#)—particularly a diet that is low in vegetables and high in processed meat and saturated fat—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. Men who smoke are also more likely to die of prostate cancer.

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, early warning signs for prostate cancer are rare. The growing tumor usually 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. Most urinary symptoms that men experience are due to other causes. However, in rare cases, typically when the disease has advanced, 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



PCF founder and chairman Michael Milken is joined by General Norman Schwarzkopf in 1998 on the Mall in Washington for “THE MARCH: Coming Together To Conquer Cancer.”

Keep in mind that urinary symptoms don't necessarily mean you have cancer. Prostatitis and BPH (**Benign Prostatic Hypertrophy**, also known as enlargement of the prostate) are common and benign diseases that can cause similar symptoms.

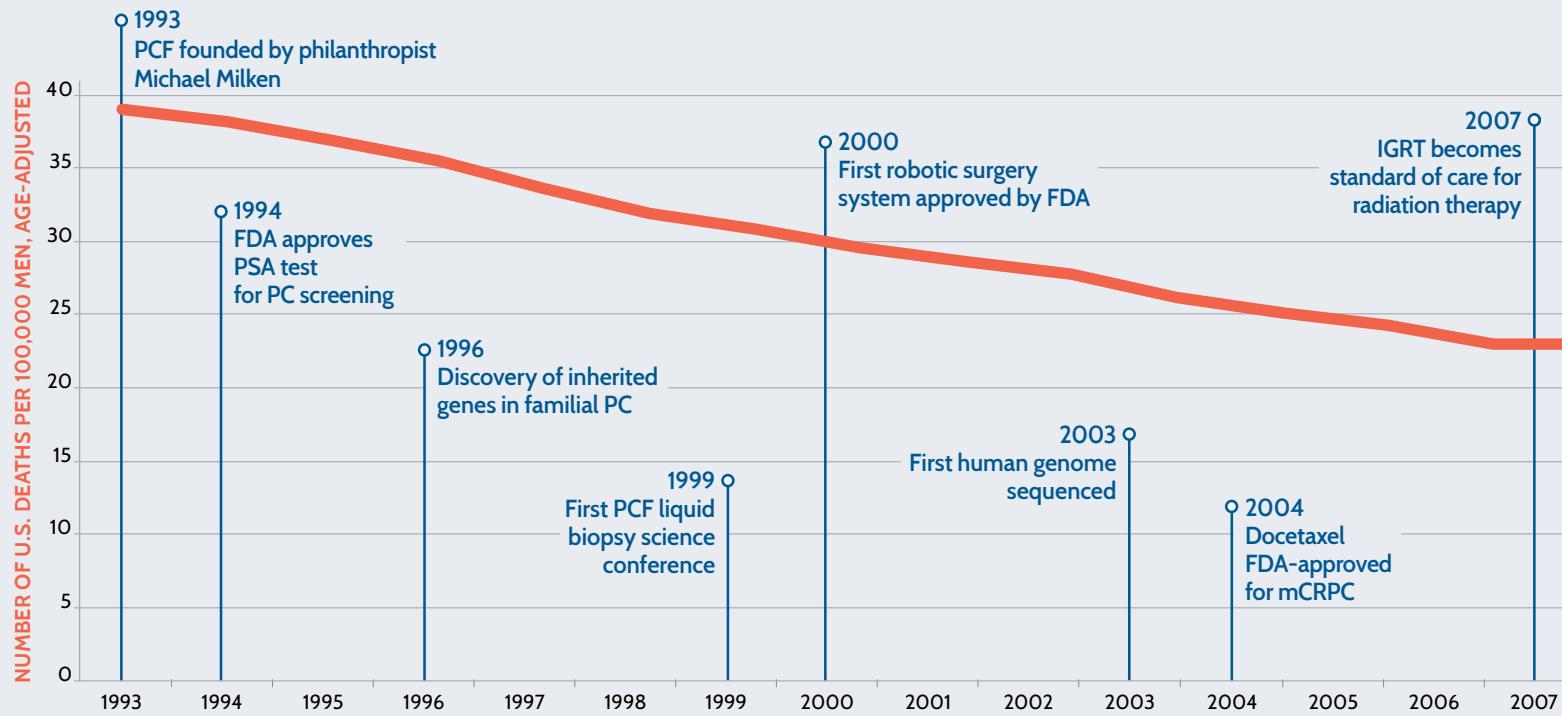
What about difficulty in having an erection? Again, this is most likely not caused by prostate cancer but by other factors such as diabetes, smoking, high blood pressure, cardiovascular disease, medications, or aging.

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 prostate tumors. Over the next 5 decades, various types of chemotherapy, radiation therapy, surgery, immunotherapy, and hormone therapy were refined.

Breakthroughs in Prostate Cancer Treatment and Practice



In 1994, the FDA approved the **PSA** blood test to detect prostate cancer in men without symptoms. Because cancer is much easier to treat when detected early, use of the PSA test for screening has resulted in more patients being diagnosed earlier, and while some debate has occurred about whether the PSA test leads to over-diagnosis and over-treatment of low-risk disease, it has substantially contributed to a greater than 50% reduction in deaths from prostate cancer over nearly 3 decades in the U.S.

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

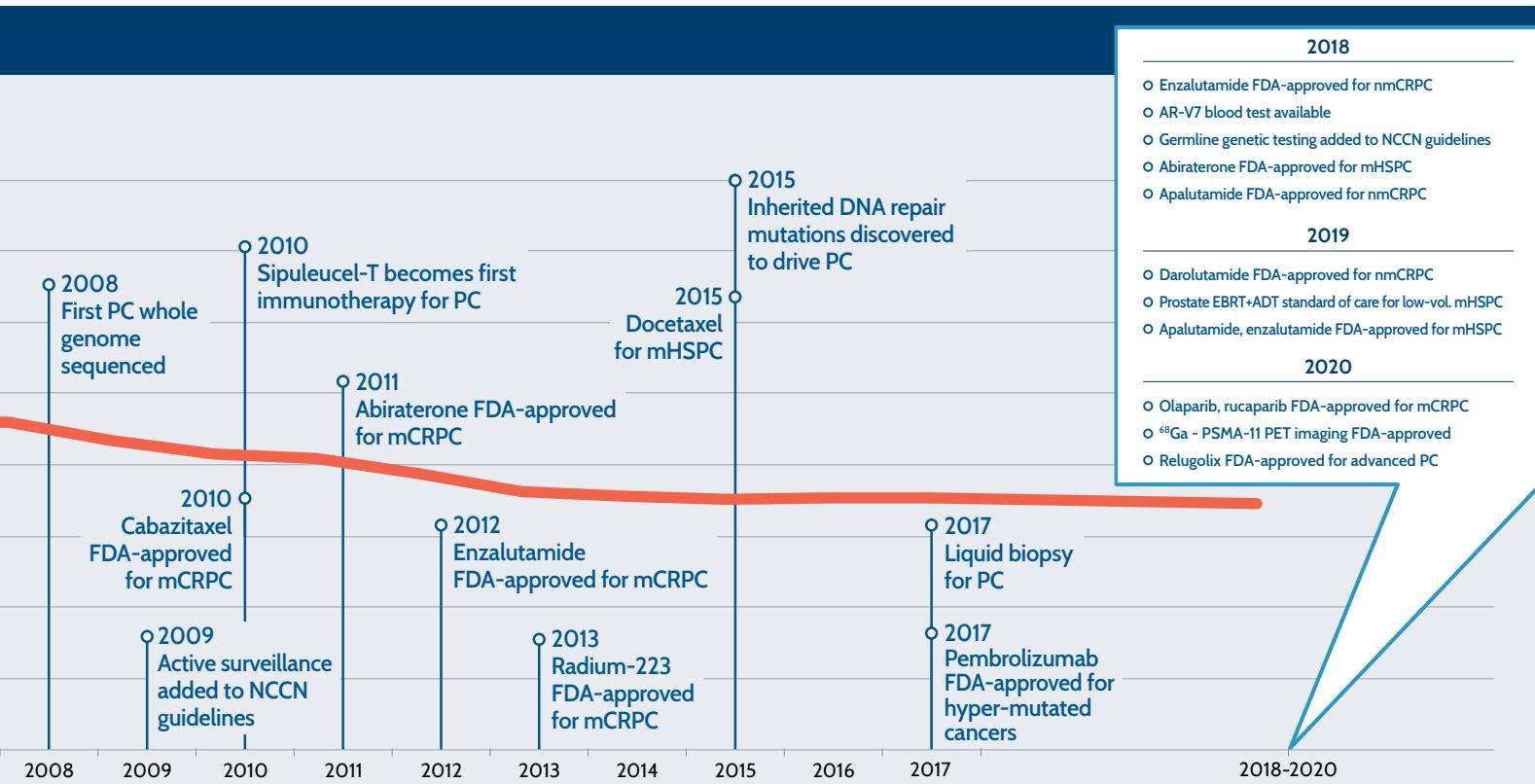
- ▶ Imaging technology to find prostate cancer earlier
- ▶ Precision radiation therapy
- ▶ Development of robotic surgery
- ▶ New FDA-approved therapies for previously untreatable cancer
- ▶ Strategies to reduce side effects and improve quality of life

Because of these improvements, since 1993, deaths from prostate cancer have been cut in half (from 39.3 per 100,000 men in 1993, to 18.9 per 100,000 men during 2015-2019). A 2019 study reported that in many countries around the world, incidence and mortality rates have declined or stabilized.

Today, **precision medicine**, which involves matching the right drug to the right patient at the right time, is ushering in a new era in treatment for prostate cancer, including DNA testing as a gold standard in cancer care. In localized prostate cancer, doctors are learning that a tumor's genomic signature may help to predict which patients may be at risk for aggressive disease. Scientists are also exploring how **immunotherapy**—using the body's own immune system to combat disease—can be used more effectively in treating and preventing 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.



The Anatomy of the Prostate

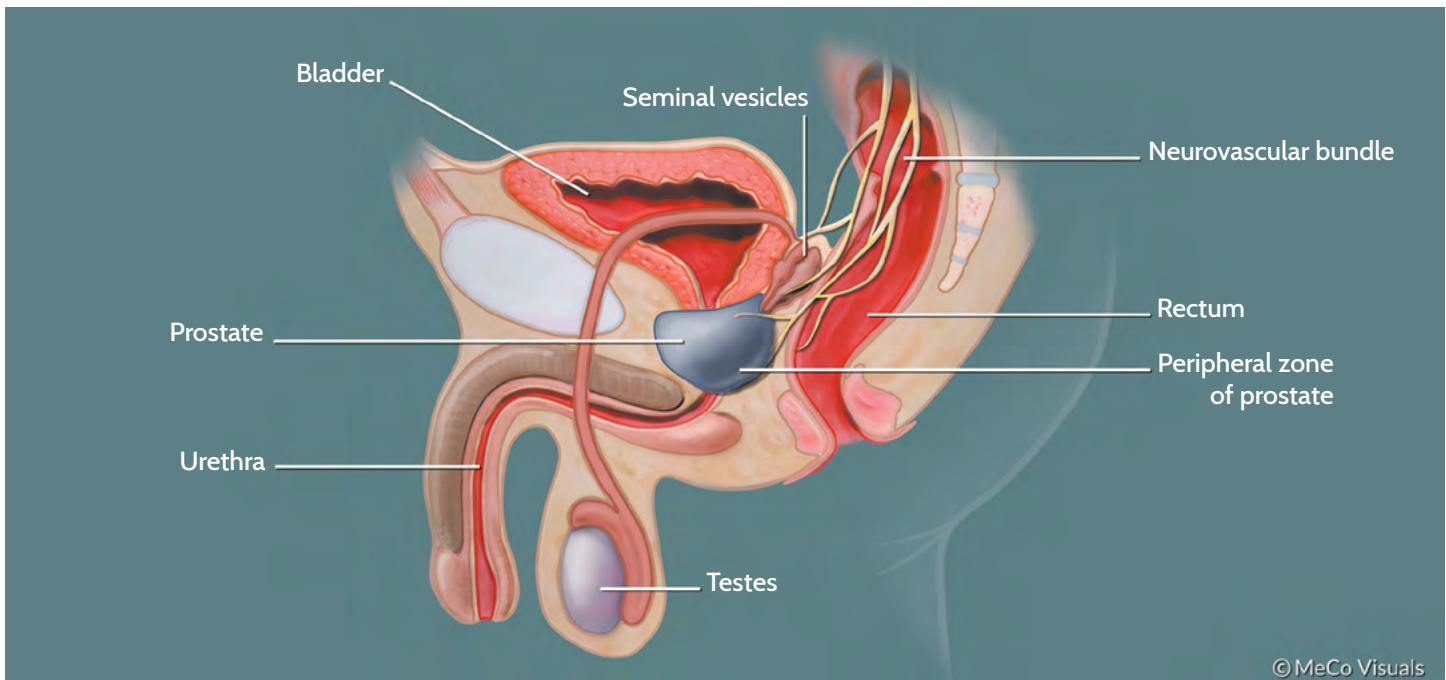
The **prostate** is a small, rubbery gland about the size of a ping-pong ball. It sits under the bladder and in front of the rectum. The prostate is only present in men. It is important for reproduction, because it supplies the fluids needed for sperm to survive and it helps push out semen during ejaculation. Sperm are not made in the prostate; they are made in the **testes** and travel to the prostate through the vas deferens (the tubes which are cut in a vasectomy procedure).

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 the physician's examination of 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 blood vessels that run along each side of the prostate, helping to drive erectile function. They travel from the lower spine all the way across the pelvis to the penis.

The Anatomy of the Prostate



Since this bundle sits very close to the prostate, it is often disturbed during prostate cancer treatment, and is sometimes directly invaded by more aggressive cancers.

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 the 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 processes **androgens** (including testosterone and dihydrotestosterone, or DHT) as part of its everyday function.

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

ANDROGENS

Androgens are hormones that are important for many male characteristics and aspects of reproduction. A common androgen is testosterone.

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.

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 sometimes in other organs such as the liver or lungs. Bone metastases are seen in 85%–90% of metastatic cases.

Even cancer that initially appears confined to the prostate may have spread. Studies using new types of molecular imaging show that over 10% of patients who seem to have local prostate cancer actually have small deposits of metastatic disease. A new, more sensitive imaging technique called PSMA PET was approved in 2020 (see page 62).

Q: “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?”

A: This does not mean you have “bone cancer” or “lung cancer.” These cells came from the prostate and “metastasized” to other areas, so they are prostate cancer cells that need prostate cancer treatment.

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. It is used as a “disease marker” to represent prostate cancer. 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.

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.

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 Grade Group classification.

“High-grade” prostate cancers are those that are composed of very abnormal cells and are 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. It is possible for any given prostate cancer tumor to contain multiple subtypes of prostate cancer. Doctors and researchers are only just beginning to use subtyping to guide treatment recommendations, thanks in part to active and ongoing research funded by the Prostate Cancer Foundation. For information on different types of tumor genetic sequencing and the scenarios in which they may be appropriate for guiding medical decisions or for contributing to research, visit pcf.org/tumortesting.

Understanding Metastasis

Sometimes cancer cells will escape the prostate and grow quickly, spreading to nearby tissue. Nearby lymph nodes are often the first place cancer spreads.

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, its rate of rising (velocity) compared with prior test results, and whether there could be another benign explanation (such as a urinary infection). As the PSA number goes up, the chance that cancer is present increases. Men whose levels are confirmed to be above 3 are often recommended to undergo a biopsy; however, this PSA level does not mean that prostate cancer is definitely there, and, conversely, some cancers may be present even when levels are lower, particularly among younger men.

THE PSA DEBATE

PSA is not a perfect test to screen for prostate cancer. Elevated levels can be caused by other prostate issues, 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 people are concerned that increased PSA screening finds tumors that are so slow-growing as to pose no long-term threat to the patient, subsequently leading to “overtreatment” and unnecessary side effects in men with low-risk cancers.

However, there is a lot of data to suggest that PSA screening, done correctly, 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. If PSA screening is used well, its value is greatly increased. It is critical that men have testing at the appropriate age and repeat PSA tests once the baseline level is known. Treatment should be reserved for men diagnosed with higher-risk cancer. The Prostate Cancer Foundation is actively funding new research into better prostate cancer screening tests that are more specific and sensitive than the PSA test.

PSA screening decisions should be made in consultation with your doctor and based on a full examination of risk factors. See also, [The Genetics of Risk](#), page 89.

In men who have 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 recurrence of 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 (**androgens** and estrogens, respectively) which are responsible for the function of the reproductive organs and the development of secondary gender 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.

Since androgens, including testosterone, fuel prostate cancer growth, prostate cancer treatment regimens may include some amount of hormone therapy—which is really “anti-hormone therapy”—that deprives tumor cells of androgens.

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.

The older term “chemical castration” is sometimes used to describe a drug treatment regimen for controlling hormone levels. **Androgen deprivation therapy** (ADT), in which medication is used to cut off the supply of testosterone to the prostate, is part of the treatment plan for metastatic prostate cancer and also for some patients with non-metastatic disease. ADT is associated with high rates of response, but it has [side effects](#), which can be more pronounced when used for years. The side effects are typically transient when given for only a few months.

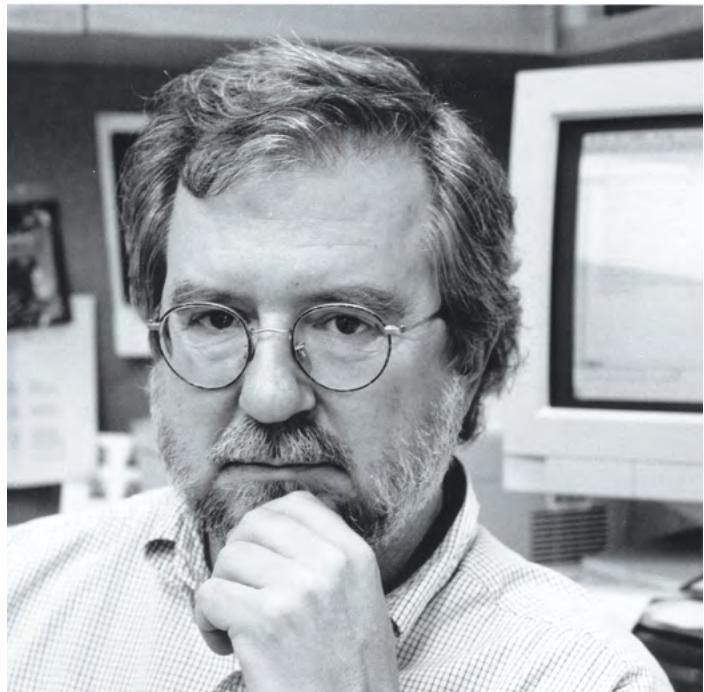
Precision Oncology

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 can now identify the mutations present in a patient’s tumor cells; this is the emerging field of [precision medicine](#), or customized treatments based on the unique characteristics of a tumor. Precision medicine is an approach to disease treatment and prevention that takes into account individual variations in genes, immune function, environment, and lifestyle.

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

As an example of what’s possible now, multiple tests using tumor tissue exist to better understand the aggressiveness of a patient’s prostate cancer. These tests may provide value beyond grade or stage in predicting whether a cancer is likely to metastasize. Also entering the field is the concept of “liquid biopsy,” where doctors can use blood tests to identify cancer mutations and treatment options. The hope is that someday, all treatment will start with tests of the cancer’s genes, proteins, and other “biomarkers,” followed by custom treatments. See [Precision Testing](#) on page 84 for more.

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. Still, a good start for anyone with metastatic, recurring, or treatment-resistant prostate cancer is to ask your doctor about precision medicine clinical trials that may be appropriate.



PCF supported Jim Allison’s early work in immunotherapy. Dr. Allison’s work on using the body’s own immune system to fight cancer earned him the 2018 Nobel Prize in Medicine.

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 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.

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, with consideration given to 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 used to describe it, a diagnosis of prostate cancer can change everything. It can be confusing, frightening, and overwhelming. It is important to remember that the word “cancer” refers to an extremely wide spectrum of biology and that, when detected early, prostate cancer tends to be less aggressive than many other cancers.

As a newly diagnosed patient, you might be torn by arguments favoring one treatment plan 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, but without knowing what a man’s needs might be. One of the most important tools you have for managing your diagnosis, both physically and emotionally, is education. The information contained in this guide can help you feel satisfied that you have made an informed decision for you and your family.

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. It is recommended that you abstain from strenuous exercise and ejaculation for 48 hours preceding your PSA, since these may artificially inflate PSA test results.

After your PSA test, your health care provider may perform a **DRE**, in which a gloved, lubricated finger is inserted into the rectum to examine the prostate for any irregularities in size, shape, and texture.

During a PSA test, a small amount of blood is drawn, and the level of PSA (prostate specific antigen, a protein produced by the prostate) is measured. The majority of men under age 50 have a PSA under 1 ng/mL. Historically, many physicians used a PSA of 3 or 4 as the borderline between “normal” and “abnormal.” We now realize this question is more complicated, and a high PSA doesn’t always mean cancer. For example, in some cases, a high

PSA may be due to infection, prostate growth, or inflammation of the prostate. However, it is also important to understand that a PSA above 3 may suggest the need for more diagnostics such as imaging, other lab tests, or biopsies.

A small but important proportion of men are at increased risk of prostate cancer due to carrying an inherited cancer risk gene or strong family history of cancer, and should consider prostate cancer screening at an earlier age. It is also important to recognize that PSA increases with age, and your PSA should be compared with normal values for men your age group. For example, the median PSA for younger men (aged 40-49) is around 0.7 ng/mL, and men with a PSA above the median are at higher risk of later developing prostate cancer. Men with inherited genetic mutations (e.g., BRCA2) may be at higher risk of aggressive prostate cancer.

Assessment of a “normal” PSA must take into account:

- ▶ The patient’s age
- ▶ Prostate size
- ▶ Results of 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
- ▶ Use of various herbal supplements, such as saw palmetto

In rare cases (fewer than 2%), men who have a normal PSA may still have clinically significant prostate cancer. Unfortunately, in most of these cases, disease does not present until it has progressed beyond the prostate and become symptomatic.

Making the Diagnosis via Biopsy

Although a high PSA may increase a doctor’s suspicion of prostate cancer, a biopsy is necessary to confirm a diagnosis. A PSA test is used to assess whether or not you should have further testing—usually in the form of imaging and/or biopsy to determine the presence of cancer. Blood and urine tests are available that may

TALKING TO INSURANCE

At PCF, we're proud to be able to tell you about the latest & greatest research, but health care systems are sometimes slow to catch up to make these advances accessible and affordable to all. It is important to speak with your insurance company directly about what is needed. Often, each cancer-related specialty (e.g., radiation, medical oncology) will have an expert on staff who is accustomed to dealing with cancer-related insurance claims. Be sure to find out if that person exists, and introduce yourself early on in this process.

If you need to talk to your insurance company about paying for a procedure that they consider to be non-standard, it's important to have on-hand the reasons why this test or procedure is critical for your health. It also helps if having the test or procedure could be so precise that it will save on future tests, procedures and other medical costs. In other words, when speaking to insurance, make sure to speak their language.

Let's take MRI fusion biopsy as an example. There is evidence that performing MRI prior to prostate biopsy is useful for risk stratification and allows targeting of the biopsy in patients with suspected prostate cancer. Urologists are putting this into practice in multiple countries. Studies have shown that using the MRI images in combination with real-time ultrasound imaging ("fusion" biopsy) is better than ultrasound alone in distinguishing between higher-grade cancer and low-grade, non-aggressive cancer. Most believe it will decrease the need for unnecessary biopsies, and, if a biopsy is needed, it will be more accurate.

Sometimes, insurance companies are hesitant to pay for a prostate MRI. The key when speaking to your insurance company is to let them know that since your PSA or DRE indicates the likely presence of disease, MRI-targeted biopsy will provide a superior map of your cancer, and may save money on future testing, when compared with the traditional TRUS biopsy. (If possible, you may consider traveling to a major cancer center with experience in prostate MRI.) That said, things are changing fast and we are optimistic that MRI will be covered by insurance for all men with an indication for prostate biopsy. This is just one example of a medical decision that may need to be informed by financial considerations. What is FDA-approved vs. what is covered by insurance is constantly changing. It's important to be an informed patient and to advocate for yourself. Feel free to provide this section of the guide to your insurance company.

provide additional information, helping you and your doctor determine whether a benign condition may be at play or whether a biopsy is warranted (see [Screening and Biopsy Decisions](#) on page 91). Some of these tests may also be combined with MRI for more precise diagnosis.

There are 3 main ways men are initially diagnosed:

1. TRUS-guided biopsy: A trans-rectal ultrasound-guided biopsy using local anesthetic is the most common way that prostate cancer is diagnosed in the U.S. An ultrasound probe is placed in the rectum to allow visualization of the prostate, then multiple needles are used to sample tissue from the prostate 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 (the MRI itself provides useful information, but cannot diagnose prostate cancer).

2. Trans-perineal biopsy: The prostate can also be biopsied under local or general anesthetic by placing a needle through the skin between the scrotum and anus (perineum). This method has a lower risk of infection, because the biopsy area is not directly contaminated with feces. While not widely used in the U.S., it is expected to become more common. Both methods of biopsy have some inherent risks of infection, bleeding, and pain.

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

Regardless of how the biopsy sample is obtained, the tissue is then examined under a microscope by a pathologist to confirm the presence or absence of prostate cancer cells.

Staging Your Disease

The goal of staging your cancer is to determine your prognosis and guide you to the most appropriate treatment. Almost all other cancers in the body use stages to describe the cancer, such as stage 1 breast cancer, or stage 3 colon cancer. This is not usually done in prostate cancer. [NCCN risk groups](#) have been the most common method to provide a patient with their prognosis.

Now, some oncologists are using a new system of staging called STAR-CAP that can provide a more accurate 10-year prognosis. While not yet in widespread use, it will provide a stage from IA to IIIB for patients who have non-metastatic prostate cancer. Stage 4 is used to describe patients that have metastatic disease beyond the pelvic lymph nodes. This transition brings us closer to the staging terminology used in other cancers. You should talk to your doctor about the specifics of your case and your prognosis.

HOW MRI SCANS MAY BE USED IN DIAGNOSIS

MRI may be used in two main ways when a man is found to have an elevated PSA. First, MRI can show suspicious areas, indicate the risk of cancerous lesions, and help to determine whether a biopsy is needed.

PI-RADS (Prostate Imaging Reporting and Data System) is a structured reporting system to evaluate for prostate cancer based on an MRI scan. The PI-RADS score is 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 equivocal
- ▶ 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

In summary, PI-RADS 4 or 5 lesions have a high probability for disease that warrants targeted biopsy for confirmation. PI-RADS 1-3 are unlikely to represent clinically significant cancer.

If it is determined that a biopsy is needed, “targeted” or “fusion” biopsies (sometimes referred to as an MRI fusion biopsy) are increasingly being offered at select centers that use MRI, in addition to the ultrasound, to better visualize tumors within the prostate and help guide biopsy needles to the areas that appear to be most suspicious.

When choosing a location for your MRI, here's why it matters: MRI technology is like fine photography. It is very different than a CT or bone scan. Just as excellent photographers will put the subject in focus and the background out of focus, this should happen with MRI as well. Thus, there is wide variation in quality of MRI; at this point in time, MRI and fusion biopsy should be performed and interpreted at a high-volume center with particular expertise in prostate MRI radiology. Research on the improvement of this technology continues.

There are 5 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**).
- ▶ The extent of the cancer revealed by the biopsy. For example, in a typical prostate biopsy which includes at least 12 needle core samples, a cancer found in 9 of the 12 cores is a higher risk than a cancer found in just 2 of the cores.

Let's look at each component in more detail.

1. PSA: A blood test.

Your doctor should have your most recent **PSA tests** and, if outdated, may order a fresh one. PSA can also be considered in relation to the size of the prostate, since a bigger prostate will normally make more PSA. Your **PSA density (PSAD)** score is calculated by taking your PSA score and dividing by the volume (size) of your prostate in grams or milliliters. PSAD values under 0.15 (e.g., a PSA of less than 7.5 for a 50-mL prostate) are usually considered reassuring.

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 original 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 replaced the Gleason score with the simpler Grade Group system ranging from 1 (low) to 5 (very high).

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

SIZE VS. GRADE

The size and grade of your tumor don't always predict its behavior over time. A small, high-grade cancer is much more likely to spread to other parts of the body than a large, low-grade cancer. In some cases, tests of your tumor's genetic material and/or proteins may be better predictors of growth over time. Consult with your health care provider to find out if further testing might be right for you.

Grade Group and Gleason Score Comparison

Risk Group	Grade Group	Gleason Score
Very Low/Low	Grade Group 1	Gleason Score ≤6
Favorable Intermediate	Grade Group 2	Gleason Score 7 (3+4)
Unfavorable Intermediate	Grade Group 3	Gleason Score 7 (4+3)
High/ Very High	Grade Group 4 Grade Group 5	Gleason Score 8 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 that can be palpated. In some cases, your practitioner 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 (i.e., 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 health care provider felt 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 (advanced).

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

Aggressive cancers (e.g., PSA >20, 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 appears less aggressive may benefit from further imaging and they should discuss this with their doctor. In the U.S., this is most commonly done with a computed tomography (CT) scan or an MRI and a bone scan. Newer and more sensitive imaging technologies are coming into the clinic, such as molecular PET imaging, including the new **PSMA PET**, which was approved for patients in 2020.

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. In the event that you are diagnosed with metastatic disease, please make sure to also read the section starting on page 66, **Therapies for Advanced and Metastatic Prostate Cancer**.



Newer studies show that performing MRI prior to prostate biopsy, using these images in a “fusion biopsy,” can offer more targeted and precise results. Check with your insurance company in advance about coverage.

5. Biopsy cores: How many were positive?

In addition to the grade of your cancer, your physician will consider the **percent positive cores** from the pathology report. This is the number of biopsy needle cores that contain cancer divided by the total number of cores sampled. In general, the higher the percentage, the more aggressive the disease. For example, if 12 biopsy cores were taken, and 4 were involved with cancer, then you would have 4/12, or 33% positive cores.

Knowing the stage of your cancer provides information about your prognosis (the likely course and outcome) and treatment options.

Consider: Tumor biomarker testing

Guidelines variably support the use of testing of your prostate tumor's genetic material, gene expression, or proteins (called "biomarkers"). Tests exist that have been shown to potentially help provide further assessment of the aggressiveness of your cancer beyond the Gleason score/Grade Group, PSA, and T-stage, including: Decipher®, Oncotype®, ProMark®, and Polaris®. Medicare usually covers the use of these tests, but private insurance payers may be less likely to cover them. Ask your physician if these tests would be right for you.

GLEASON 3+3

Today, pathologists do not give a grade below Gleason 3+3 (Gleason 6, or grade group 1) when scoring prostate cancer tumors. If you have prostate cancer, the lowest Gleason score you will receive is a 6. Many, but not all, prostate cancers in this Gleason range may be slow-growing and are appropriate candidates for active surveillance. Consult your doctor or practitioner for more information.

SELECTING YOUR TREATMENT

There is no "one size fits all" approach for precise treatment of prostate cancer. For some men this feels liberating; for others, it can be confusing and frustrating.

To add to the confusion, your doctor may not recommend treatment at all (also termed observation or "watchful waiting") or might recommend putting you under "[active surveillance](#)" (see page 35). It's important to learn as much as possible about the options available and, in conjunction with your healthcare team, make a shared 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 personal 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 treatment option based on risks, benefits, and quality of life

For men who are sexually active, concerns about post-treatment potency are often top of mind. If preserving your ability to have erectile function is a priority for you, make sure to discuss this with your doctor *before* selecting a treatment plan. It is also essential to realize, however, that many interventions are available to help with sexual function both before and after prostate cancer treatment.

The vast majority of prostate cancers are diagnosed by urologists, who perform the biopsies. After a diagnosis of prostate cancer, you should see both a urologist (preferably a urologic oncologist) and a radiation oncologist to review all of your treatment options. In some cases, a medical oncologist should also be seen to review additional systemic therapy options.

FERTILITY OPTIONS

For men who are hoping to father a child in the future, it is vital to discuss fertility preservation and sperm cryopreservation with your physician before you undergo any treatment. You can learn more about these issues in the [Possible Side Effects: Fertility](#) section on page 52.

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 practitioners might be right for you.

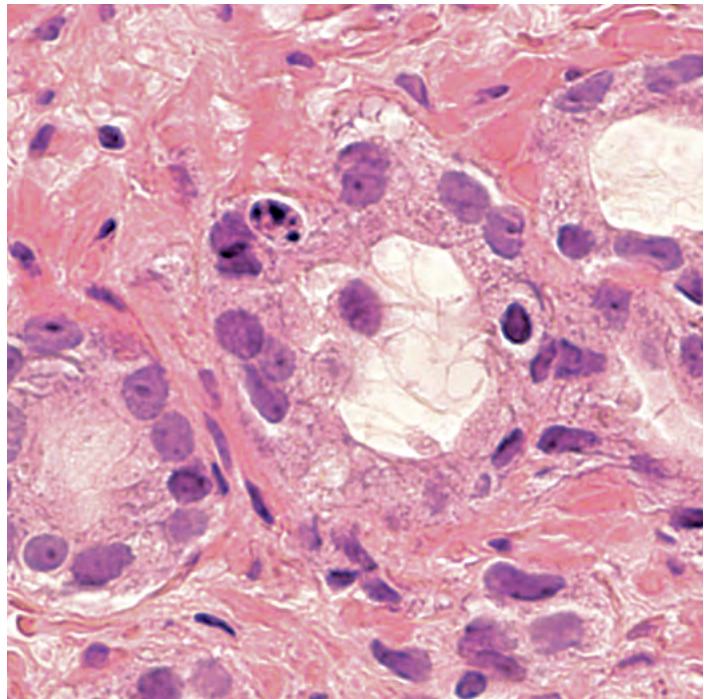
In general, for nearly all cases of newly diagnosed localized prostate cancer, the chance of “cure” is the same whether you have radiation therapy or surgery.

For men with high-risk or metastatic disease, your doctor may now recommend biomarker testing of your tumor and/or genetic testing for an inherited mutation to determine if there is a targeted therapy for your type of disease. Talk to your doctor about whether genetic and/or tumor testing is right for you, or visit pcf.org for more information.

It is also important to remember that, often, physicians, books, blogs, and websites present only half of the story, favoring one treatment option. This leads to a great deal of misunderstanding. The best thing you can do is to read through this patient guide and make sure you seek the advice of a urologist, a radiation oncologist, and, based on the stage of your disease, a medical oncologist.

In the U.S., 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 associated [side effects](#), logistics, or personal desire. Your team of doctors will evaluate your type of prostate cancer to develop a treatment plan that may include surgery, radiation, some combination of both, or neither. The main difference between surgery and radiation therapy relates to quality of life, side effects, and logistics.



The grade of a cancer refers to how abnormal the biopsy tissue appears. Low-grade cancers more closely resemble normal prostate tissue. Higher grade means more aggressive cancer.

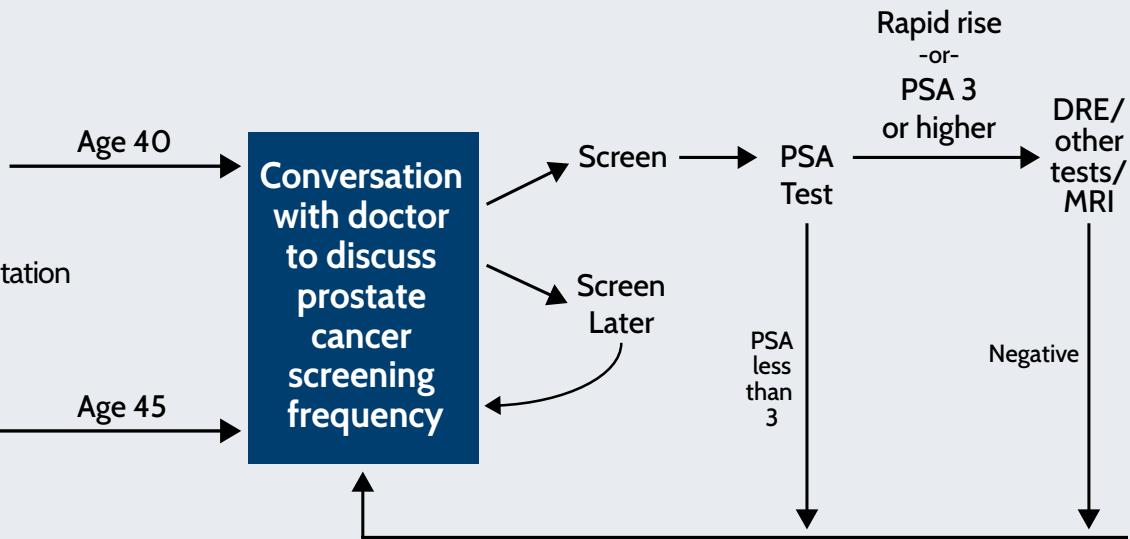
Your doctor will use information from many sources to determine how aggressive your cancer looks and whether it has spread outside the prostate.

PROSTATE CANCER PATIENT TREATMENT PATHWAYS

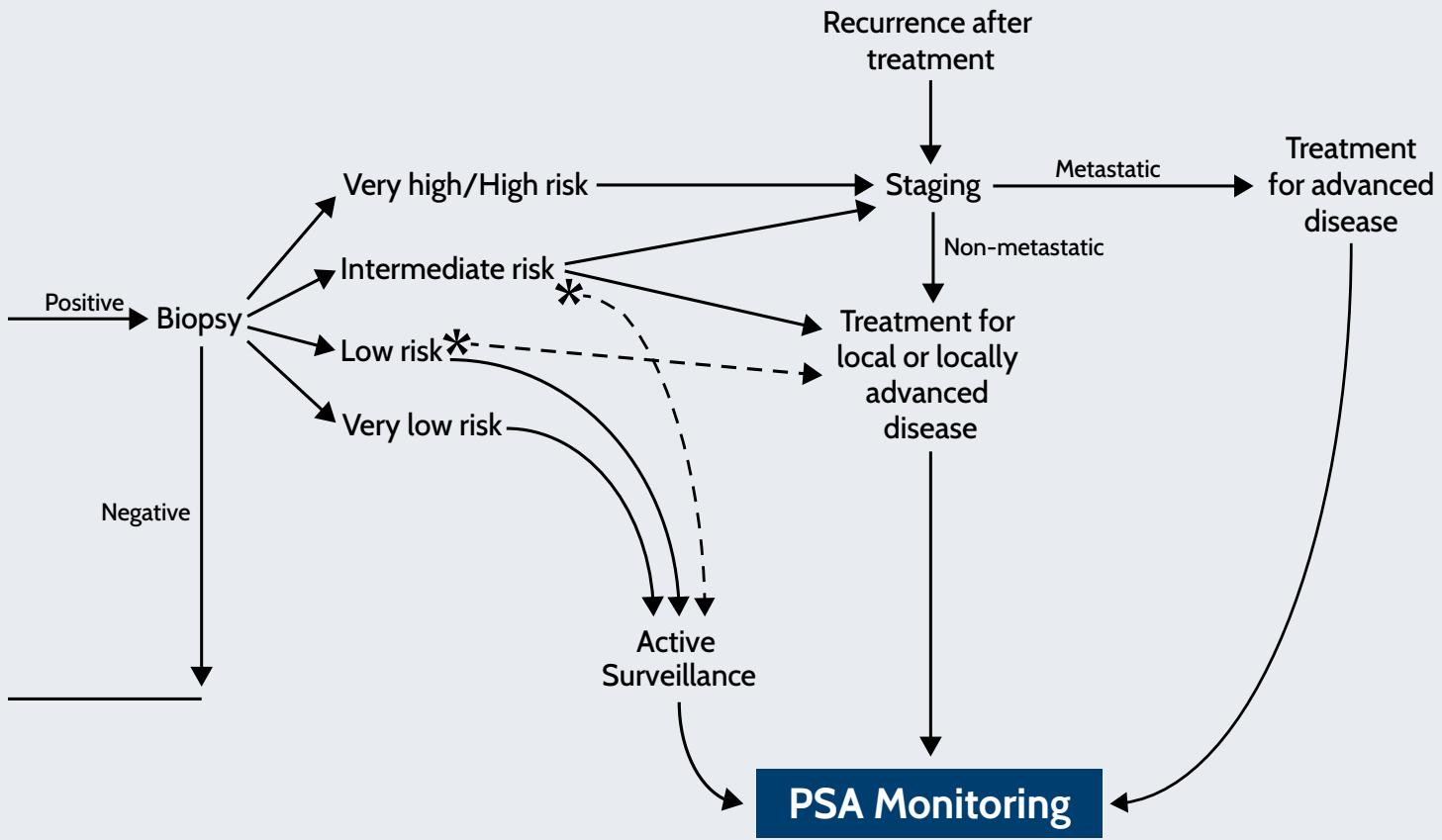
Men who:

- ▶ Are Black
- ▶ Have a family history of prostate cancer
- ▶ Have a strong family history of other cancers
- ▶ Have a known gene mutation (e.g., *BCRA*)

Everyone else



No two patients are exactly the same, and every man's prostate cancer journey is a little bit different. This chart details some of the most common paths followed in diagnosis and treatment of prostate cancer. All men are encouraged to have a conversation with their doctor about when to begin prostate cancer screening, especially if you have a history of prostate cancer in your family. If you are diagnosed with prostate cancer, talk with your doctor about what tests and treatments might be right for you.



*For select patients; consult your doctor

Find more information about each of these topics on the pages listed below:

- Screening: page 89
- Diagnosis: page 17
- Risk groups: page 33
- Staging: page 19
- Active Surveillance: page 35
- Treatment for local/locally advanced disease: Chapter 3
- PSA monitoring: page 59
- Treatment of recurrent and advanced/metastatic disease: Chapter 5

For high-risk or aggressive cancers, most patients will have the best outcomes from receiving “multi-modal” therapy, that is, more than one treatment (i.e., surgery and post-operative radiotherapy with hormone therapy, or radiation with hormone therapy). These combination treatments provide the best chance of long-term disease control. Every patient has a different cancer and different priorities with regard to what aspects of [quality of life](#) are the most meaningful, so it’s important to take time to understand and process your diagnosis as well as the therapy options available to you.

Remember, it is always okay to get a second opinion, whether or not treatment is needed. If possible, choose urologic oncologists, radiation oncologists, and medical oncologists at high-volume, prostate-focused cancer centers.

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 prostate cancer specifically. 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 affiliated with a reputable 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? Did they seem rushed, or do they seem interested in what is important to you?
- ▶ Are they covered by your health insurance? If not, can you change insurance?

Remember:

- ▶ Take your time
- ▶ Get second or even third opinions if you don’t feel comfortable
- ▶ Be careful of advice that seems highly opinionated, e.g., “surgery is the best” or “radiation is the best” or “eat this herb and your cancer will be cured.” Avoid any health care provider who seems like he or she is “selling” something
- ▶ There are many books, websites, and blogs written by “experts” that claim their treatment is best: be cautious of these. For accurate information, use 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

If you have a good relationship with your primary care provider, you may opt to stay in close touch about your diagnosis, treatment, and decision-making. Primary care providers can offer help to think about the big picture of your health, and can help you work through complicated decisions.

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 key.

Tips for Partners, 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 urinary, bowel, or sexual function
- ▶ It is normal to experience loneliness and fear—seek out support groups for partners and caregivers, in addition to encouraging the patient to attend a support group

Tips for Young Children

- ▶ Keep children informed; treat them as part of the team
- ▶ Answer questions honestly, as age-appropriate
- ▶ Be realistic but optimistic in your communications
- ▶ For older children, you might encourage them to join a support group. For younger children, consult your pediatrician or 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 politely 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.

Doctors and Healthcare Practitioners Involved in Prostate Cancer Diagnosis and Treatment

Urologists specialize in problems affecting the urinary tract (kidney, bladder, prostate, urethra, penis, and related organs). They are surgeons, but may have no formal dedicated training in cancer.

Urological Oncologists are urologists who specialize in surgery of cancers of the urinary tract (kidney, bladder, prostate, penis, and related organs).

Radiation Oncologists specialize in treating cancer patients with radiation therapy (external, internal, and systemic forms of radiation therapy).

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

Radiologists and Nuclear Medicine Physicians specialize in interpreting your imaging scans, 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.

Nurse Practitioners (NPs) and Physician Associates (PA) are “physician extenders” who work closely with physicians to help you with your care. They often are the first line of response for your questions and concerns, and also manage some aspects of routine follow-up care.

Oncology Nurses administer therapies and monitor your overall health as you progress through your treatment.

Dietitians and Naturopathic Doctors counsel patients on nutrition and wellness issues, including complementary medicine and mind-body awareness, 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.

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 pcf.org/fr-caregivers.

You

Sadness, fear, sleeplessness, and anger are all normal early emotions after receiving 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.

To join an online support group, please visit pcf.org/groups. For more information on counseling resources, visit cancercare.org. To find a local prostate cancer support group in your area, visit [UsToo.org](http://ustoo.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. When diagnosed, the first instinct may be to choose a therapy from the first provider you see who promises to eradicate the disease. Many men experience a strong desire to just "get it out" surgically. But it is important to take the time to investigate your options.



"Looking back, I wish I'd gotten more perspectives. It would have been better to really talk about all of my options." – Patient

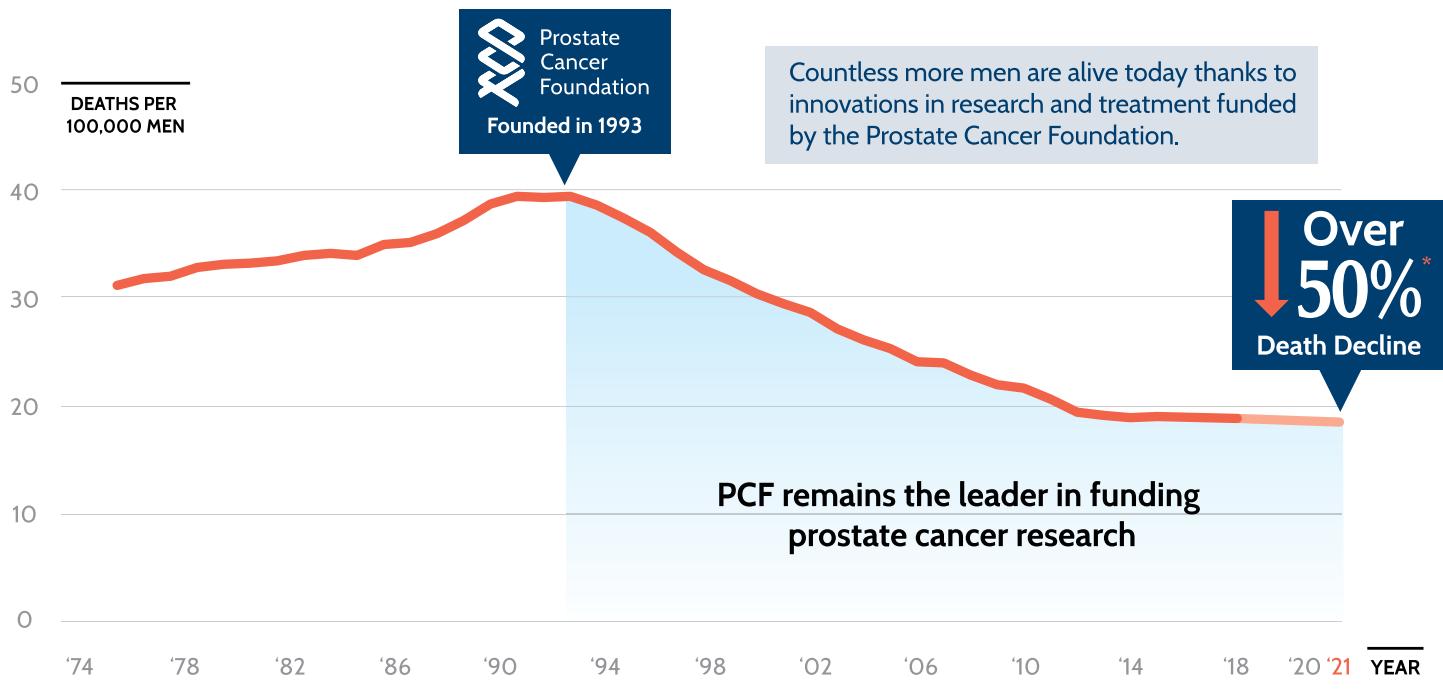
Depending on the features of your cancer, and your age, overall health, and personal family circumstances, [active surveillance](#) may be the right choice for you. [Side effects](#) of each treatment are also important to consider, and only you can know what potential outcomes are acceptable to you. Regardless of which treatment you choose, it's important to observe recommended [diet and lifestyle modifications](#) from the moment you are diagnosed.



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

For men who are sexually active, remember that stress can affect erectile function. In fact, a diagnosis of any type of cancer can disrupt sexual function for men and women. The maximum sexual function you could potentially regain after treatment will be based on your levels before diagnosis. Seek expert counsel for you and your partner on how to support each other through therapy and recovery.

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! The decision is very unique to each person; it may not be right for your brother, your friend, or any of the 20 other people you consulted, but it may be your best choice on the road to 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 work with your medical team to identify 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/risk group? 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 need to have 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 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? To what extent should I worry about impotence, urinary leakage, or rectal problems, and are the risks different with different treatments?

How do my baseline urinary, sexual, or bowel function affect my treatment decisions, if at all?

When will I see a radiation oncologist and/or medical oncologist to understand all of my options? 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?

What will my pre/post-surgery rehabilitation plan look like?

How likely is my cancer 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
- ▶ Radiation therapy

Choosing the best treatment 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.

For men whose disease appears more aggressive, certain treatment combinations may be recommended. For example, radiation therapy is sometimes combined with [hormone therapy](#); surgery often requires radiation therapy afterwards, with hormone therapy.

Each first-line treatment has different risks and [side effects](#). It is critical that you ask your doctor to outline your risk for all possible outcomes of all possible treatment options before you select your path. For example, while one man might be more concerned about how fast he can get back to work, another man might be more interested in maintaining long-term erectile function or urinary continence.

TWO THINGS TO WATCH OUT FOR

Hormonal therapy by itself is not a standard treatment option for localized prostate cancer.

Investigational treatment options for localized disease—such as [cryotherapy](#) and high-intensity focused ultrasound ([HIFU](#))—have thus far not demonstrated the same long-term success as surgery or radiation therapy in large clinical trials. They are typically not recommended by national guidelines outside of a clinical trial and may not be covered by insurance. Patients electing cryotherapy or HIFU should consider receiving these treatments in a clinical trial.

RISK GROUPS

Health care providers 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 cores are positive, ≤50% of any core is involved with cancer, and PSA density is <0.15.

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 is >20, or grade group 4 or 5 (Gleason 8 to 10). There is also a subset of very aggressive tumors 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.

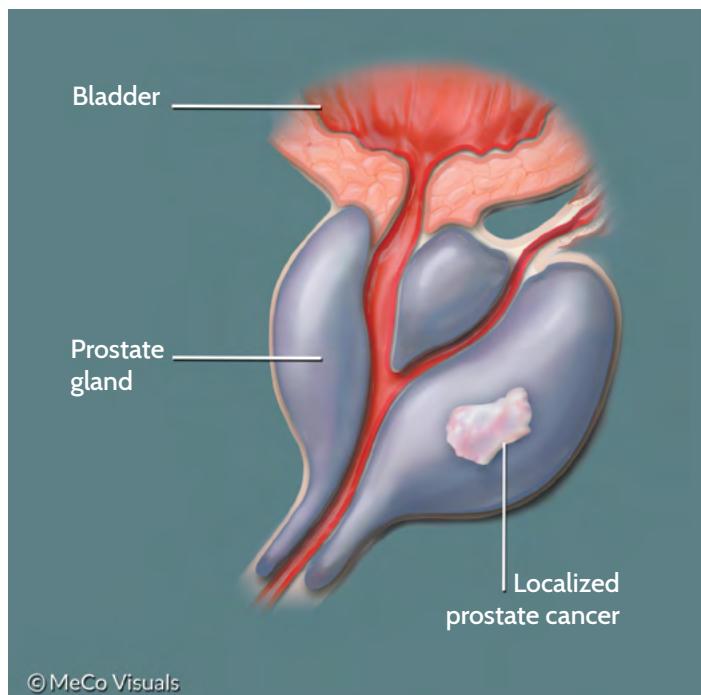
These risk groups are not perfect indicators of your risk for developing recurrent, aggressive prostate cancer. Currently, there are extensive, ongoing efforts to develop tests that can aid physicians in more accurately telling the difference between cancers that will become fatal and those that will sit in the prostate without spreading. For example, your doctor may use the newer STAR-CAP staging tool to better understand your prognosis after standard-of-care treatment.

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.

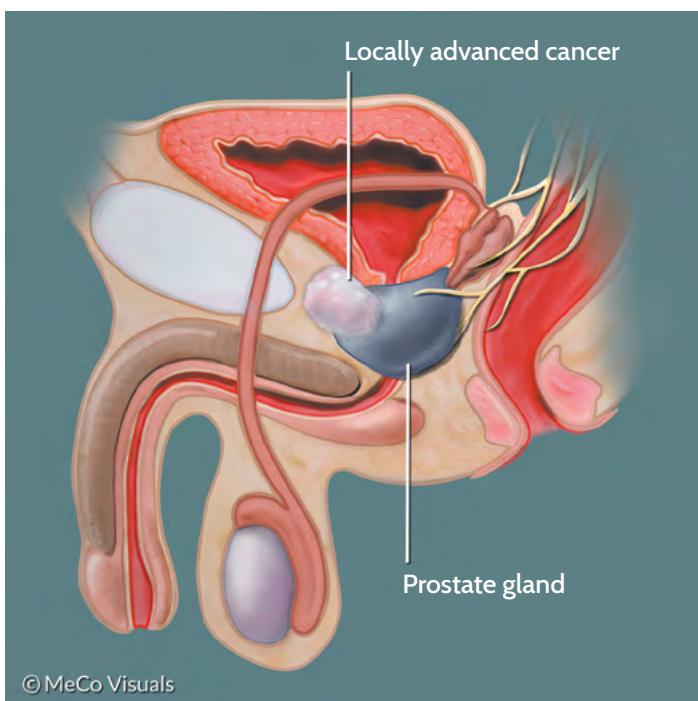
How are Risk Groups Determined?

Risk Group	Criteria	Treatments	Notes
Very Low			
	Grade group 1, PSAD <0.15, fewer than 3 cores are positive, and ≤50% of any core is involved with cancer	Active surveillance or watchful waiting; men with a life expectancy >/=20 years may consider radiation therapy or surgery	Active surveillance is strongly recommended for nearly all men in this risk group. Immediate treatment has not been shown to help men with very low-risk disease live longer.
Low			
	T1-T2a stage Grade group 1 PSA <10 ng/mL	Active surveillance or watchful waiting, depending on life expectancy	Select patients with higher-volume low-risk disease with other adverse genomic or imaging features 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 similar 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 positive for cancer	Radiation therapy + short-term hormone therapy Surgery +/- post-operative radiation therapy	Cure rates are similar between surgery +/- post-operative radiation therapy vs. radiation therapy + hormone therapy.
High			
	Any one of the following risk factors: Grade group 4 or 5 T3a stage PSA >20	Radiation therapy + long-term hormone therapy Surgery +/- post-operative radiation therapy +/- hormone therapy	Cure rates appear equal between surgery + post-operative radiation therapy vs. radiation therapy + hormone therapy. Post-operative radiotherapy is commonly needed after surgery for men with high-risk prostate cancer (>50% on average).
Very High			
	Any one of the following risk factors: T3b-T4 stage Primary Gleason pattern 5 >4 cores with Grade Group 4 or 5	Radiation therapy + long-term hormone therapy Surgery + post-operative radiation therapy +/- hormone therapy	The most common treatment for this patient subgroup is radiotherapy + hormone therapy. Very well-selected and informed men may consider surgery as part of a clinical trial, or may consider surgery in the hands of an experienced, high-volume prostate cancer surgeon with the knowledge that they likely will require additional post-operative treatment with radiotherapy and potentially hormone therapy.

Localized vs. Locally Advanced Prostate Cancer



© MeCo Visuals



© MeCo Visuals

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

For men with low-risk disease, active surveillance has emerged as the preferred standard of care.

Active surveillance is based on data that [low-risk](#) prostate cancer has not been shown to cause harm or decrease life expectancy. This is important because both surgery and radiation—which are the most common treatments for localized prostate cancer—can have side effects that decrease a man's quality of life.

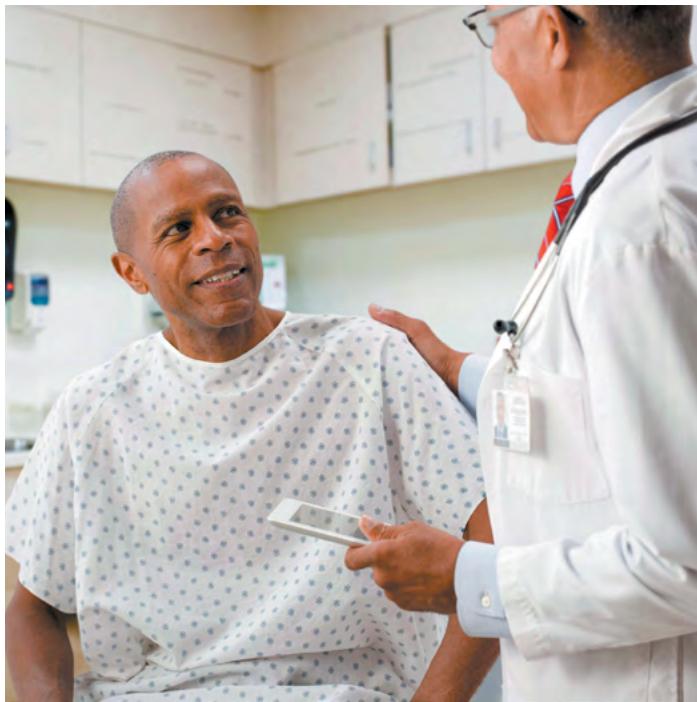
Active surveillance is not “no treatment,” but rather a strategy to follow the cancer closely so that “treatment” is deferred to only “if and when” it may be needed.

Men on active surveillance will usually have a [PSA](#) blood test done twice per year and a DRE annually, with repeat biopsies every 1 to 5 years. MRI is also being incorporated to help determine the timing of, and provide guidance for, the repeat biopsies.

If or when test results indicate that your cancer has begun to progress, treatment such as surgery or radiation may be warranted, and in a large majority of cases will still be curative.

Over 30% of men have prostate cancers that are so slow-growing that active surveillance is a better choice than immediate treatment because it allows them to avoid side effects from treating disease that will never cause them harm. In fact, prostate cancer is the only one of the top 10 most common types of cancer for which so many patients do not require aggressive immediate treatment.

A Johns Hopkins study found that, even after 15 years, less than 1% of men with low-risk prostate cancer who chose active surveillance developed metastatic disease. This is identical to the rate one would expect if all of these men were treated with surgery or radiation. But remember: the key to successful outcomes like these is to make sure you are monitored regularly and carefully for signs of progression.



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

QUESTIONS TO ASK YOUR DOCTOR IF YOU ARE CONSIDERING ACTIVE SURVEILLANCE

- ▶ What type of testing will be required if I do active surveillance?
- ▶ How frequently will I be tested?
- ▶ What is my baseline PSA number, and what number would be concerning?
- ▶ What are my options if a future test indicates that the disease has become aggressive?
- ▶ What are the chances that my cancer will progress in the next 10 years if I defer immediate treatment?
- ▶ How does my family history of cancer factor into this decision and the risk of progression? Should I have genetic testing for an inherited mutation?

The ideal candidate for active surveillance has low-risk prostate cancer.

Who Should Choose Active Surveillance?

Active surveillance may be right for you if your cancer is in Grade Group 1 (Gleason 3+3), PSA <10, and the cancer is confined to the prostate and/or cancer that is very low volume when biopsied (see page 34 for a full comparison of risk groups). Selected cases with low-volume Grade Group 2 (Gleason 3+4) tumors may also be considered for active surveillance. Sometimes, commercial tests—such as Decipher®, Oncotype DX GPS®, and ProLaris®—are used in decisions about active surveillance in situations that are less clear. Research is ongoing to understand the best use of these tests. They are currently covered by Medicare and (less often) by private insurance companies, so check with your insurance provider to confirm if you are covered if your doctor recommends one of these tests. It is always a good idea to talk with your doctor about your choices, and see if active surveillance might be right for you.

Often men wonder if they are the “right” age for active surveillance. There is no right answer to this question.

For younger men who have the potential to live for quite a long time after diagnosis, it is important to think about preserving quality of life while making sure to identify high-risk prostate cancer if it develops. A man with a less aggressive form of cancer may be able to stay on active surveillance for many years, thus delaying side effects such as urinary incontinence, erectile dysfunction and others.

For men who might have a shorter life expectancy, either because of older age or because of other medical problems, active surveillance, which involves frequent testing, may actually be too aggressive. For these men, watchful waiting may be more appropriate. **Watchful waiting** is a more passive strategy which avoids repeat biopsies and leads to non-curative or palliative treatments only if the cancer starts to cause symptoms.

A man who is currently battling other serious disorders or diseases—such as very advanced heart disease or other cancers—should consult with his doctor about whether watchful waiting would help him avoid unnecessary treatment and would be recommended. For everyone else, as with any treatment for prostate cancer, shared decision-making with a physician is necessary, and maintaining a healthy lifestyle is advised to maximize results.

SURGERY

Removing the entire prostate gland and seminal vesicles through surgery, known as a **radical prostatectomy**, is an option for men with intermediate or high-risk cancer that has not spread.

Open radical prostatectomy has been the traditional 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 has become far less common than robotic surgery.

Today, **robot-assisted laparoscopic radical prostatectomy** is very popular in the U.S. 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.

Compared with open surgery, robot-assisted surgery may be associated with less bleeding, a bit less pain, fewer short-term complications, and equivalent cancer cure rates. Preservation of urinary and sexual function recovery depends more on the surgeon's skill and patient factors than which method of surgery is chosen.

SURGICAL MARGINS

After your doctor removes the prostate, a pathologist will examine the cells under the microscope. A final grade and stage will be determined at this point.

Your margins are clear if no cancer cells are seen at the outer edge of the tissue that was removed.

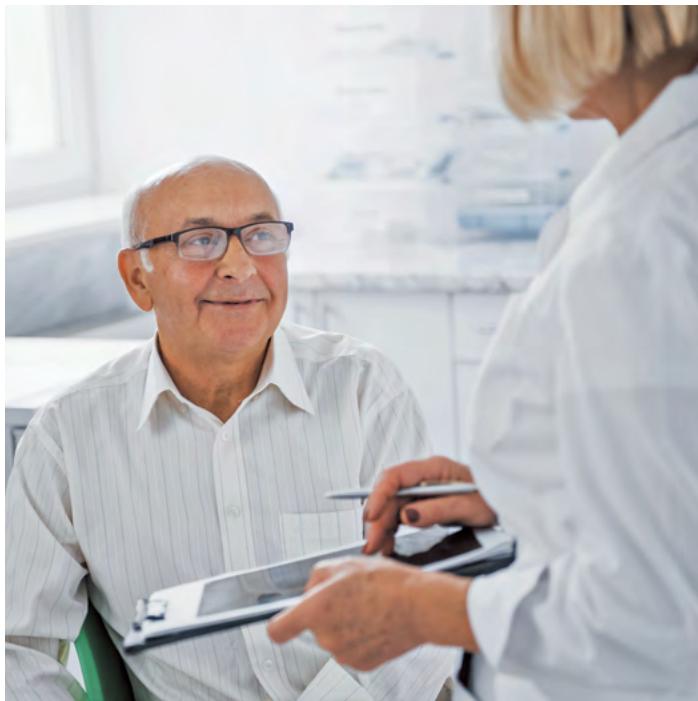
The margins are positive if the cancer extends all the way to the edge of the tissue that was removed.

Positive margins can imply that some cancer was left behind, and can be used to help determine the need for radiation therapy. But a positive margin isn't always a cause for alarm, especially in lower-grade cancers.

Patients with other problematic pathology features at surgery (e.g., extension of cancer beyond the capsule or invasion of the seminal vesicles or lymph nodes) may require additional treatments such as radiation and/or hormonal therapy. These decisions are usually made after the first PSA is checked 6 to 8 weeks after surgery.

Remember: make sure to request a copy of your pathology report; ask your doctor to explain it and to discuss options based on your results.

Whether open or laparoscopic/robotic surgery is chosen, patients typically go home after an overnight stay in the hospital with a bladder catheter to help drain urine for 7 to 14 days. For a full discussion of side effects, including those after surgery, see page 50. Of note, men with BPH symptoms (such as urinary frequency or urgency or a weak urine stream) may experience improvement in these symptoms after surgery.



There are many different types of radiation therapy available today. Be sure to use this guide to talk to your physician about which option might be best for your prostate cancer.

There are three other second-line therapies that may be given in conjunction with surgery. You should discuss the risks and benefits of each with your doctor, once your pathology report is available.

- ▶ **Adjuvant radiation therapy** (started 4–6 months post-surgery, without evidence of rising PSA) may be given to men with [high-risk](#) prostate cancer who have cancer that has penetrated through the prostate capsule, into the seminal vesicles, and/or who have positive margins after surgery. This may reduce the risk of recurrence, but may also increase the risk of side effects. Many men, but not all, can safely avoid adjuvant radiation therapy, and closely monitor their PSA to determine if they will need early salvage radiation therapy.
- ▶ Another strategy is to use radiation only if PSA levels rise to 0.1 or 0.2 ng/mL; this is referred to as **salvage radiation**, which should be done soon after the first PSA becomes detectable. Hormone therapy may be given along with the radiation therapy. The Decipher® test is

now recommended to be used for men considering adjuvant radiotherapy, and may also help guide the use of hormone therapy with salvage radiotherapy. This test may help you and your doctor decide if you would benefit from immediate radiation therapy or the addition of hormone therapy.

- ▶ **Hormone therapy** may also be recommended for men who have cancer found in their lymph nodes at the time of surgery; in this context, hormone therapy after surgery has been shown to help patients live longer.

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.

RADIATION

Radiation involves the precise 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. Recent evidence proves that radiation may help men with metastatic disease live longer, and is discussed on page 70.

Although modern technology is used to minimize damage to surrounding non-cancerous cells, normal tissue may be affected, causing side effects. 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. Ideally, seek a radiation oncologist who specializes in the treatment of prostate cancer.

External Beam Radiation Therapy (EBRT)

EBRT is the most common type of radiation therapy. In EBRT, CT scans with or without MRIs are used to map out the location of the tumor cells, and X-rays are targeted to those areas. Your “mapping” scan will help your radiation oncologist to locate the precise anatomy of your prostate, rectum, and bladder so that radiation technicians and physicists can work with sophisticated computer treatment systems to design a personalized radiation plan for you. There are many types of EBRT, each with its own advantages and disadvantages (see inset at right).

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

Since it is non-invasive, there is no down time or healing time. You can be physically and sexually 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 weeks after treatment completes, these symptoms generally begin to improve, though as with any treatment, a small percentage of men can have persistent problems with urinary and/or bowel function.

Most 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 less erectile dysfunction, and for those that do have erectile side effects, it develops more slowly. For more details, see [Possible Side Effects: Sexual Function](#) on page 52.

Treatment Durations

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

- ▶ **Conventional:** For decades, radiation therapy was delivered every day (Monday through Friday), for a total of 40 to 45 treatments over 8 to 9 weeks. This treatment is less commonly used today, but has shown excellent long-term disease control on par with newer approaches called “hypofractionated radiation.”

- ▶ **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. This is considered by national guidelines to be the current standard of care for many men with localized prostate cancer.

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. This treatment is usually delivered in 20 to 44 treatments.

Image-guided radiation therapy (IGRT) is a form of IMRT, but is 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 markers 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 is one of the newer forms of radiation therapy and it is not yet available at all treatment centers. Studies have shown that when given at a major cancer center by experienced practitioners, it is safe, just as effective, and has very low side effects, similar to the longer course of 9 weeks of radiation therapy. Talk to your doctor for more information.

► **Ultra-hypofractionation:** This is another name for SBRT, or treatment delivered in about 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. At many centers of excellence this is the standard of care. However, not all centers can safely provide this treatment, and not all patients are good candidates, so make sure to consult your doctor. This type of radiation has been compared head-to-head with the traditional 8 to 9 week course of radiation and shown to have similar cure rates and side effects. Ongoing trials are assessing whether it is superior to surgery.

Brachytherapy

Brachytherapy involves an invasive procedure under anesthesia to place 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 (made of radioactive iodine or palladium, and coated with titanium) 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.

Brachytherapy by itself is usually used only for favorable [intermediate-risk](#) patients. Patients with unfavorable intermediate and high-risk prostate cancer may also receive a combination of external beam

radiotherapy plus brachytherapy, and should also receive the addition of hormone therapy. 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.

As the use of IGRT and SBRT have increased, brachytherapy is now less commonly used. As of 2016, less than 5% of patients with prostate cancer are treated with brachytherapy. Some patients prefer it because it doesn't require daily visits to the treatment center. Although brachytherapy can deliver very high doses of radiation, it also has been shown to have higher rates of side effects in recent trials compared to EBRT. LDR brachytherapy has been shown to increase urinary side effects by about 3-fold compared with EBRT, and might also have worse rectal side effects.

Side effects from brachytherapy can include erectile dysfunction, urinary frequency, urinary obstruction with need for catheter use, and rectal injury with bleeding. Patients who have large prostates or 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 sometimes 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. In December 2020, the FDA approved a new oral form

(continues on page 43)

► WORKSHEET: LOCAL OR LOCALLY ADVANCED PROSTATE CANCER

If you're a numbers guy, here's a place for you to record where you were at the time of initial diagnosis, and any notes from your doctor or outstanding questions about treatment options.

Age at diagnosis: _____

PSA #1: _____

PSA #2: _____

Date: _____

Date: _____

Biopsy Date: _____

Stage: _____

Grade Group: _____

Gleason Grade: _____

Number of positive cores in biopsy: _____

Risk Group: _____

SHIM score before treatment: _____

(Go to pcf.org/SHM to find your score)

Other tests or test results your doctor may have recommended:

Pre-Biopsy	Post-Biopsy

Notes and questions about treatment:

Treatment option	Schedule/frequency/side effects/questions

Other notes:



► WORKSHEET: TAKING CARE OF YOURSELF DURING CANCER

Being diagnosed with cancer is tough—at any age, at any stage, at any time.

Often patients experience a bit of brain fog at diagnosis. This can be anything from a loss of focus to hopelessness. Remember: most prostate cancer is 99% treatable if detected early. Still, it's a lot to process.

Self-care is probably not at the top of your list right now, which is why this list is here to remind you to continue (or start!) to take good care of yourself. No matter what stage of the cancer journey you are at, your body will perform better if it's well taken care of. For example, quitting smoking before cancer surgery lowers complications and speeds recovery time. During cancer treatment, yoga can reduce symptoms of pain and fatigue. Long-term, regular exercise can reduce your risk of cancer recurrence or death from cancer.

PCF's *The Science of Living Well, Beyond Cancer* advocates on your behalf. If you don't have the time or inclination to download the guide, here's a quick checklist:

- ✓ **Put this list on your fridge.**
- Know what's coming. Talk to your doctor to see if any of the treatments you've chosen, or might choose, could affect your appetite or energy levels.
- Don't be afraid to ask. If you're not sure what the doctor recommends in terms of rest, exercise, and nutrition during treatment, don't be afraid to ask for details, or even a referral to a registered dietitian who specializes in cancer patients.
- Prepare for what's before you. Carve out time in your schedule (or solicit help) to get to treatment, shop for healthy food, exercise daily, and rest.

Talk to your doctor before starting any new or “in-treatment” routine. In so far as your treatment protocol and recovery instructions allow, stick with PCF's three pillars of healthy living:

Relax	Exercise	Eat Real Food
<ul style="list-style-type: none">✓ Try yoga or meditation to help calm your body and mind. There are lots of online classes for free.✓ Get lots of sleep, since this is the time when recovery happens. If the cancer has got your sheep all tied up, check with your doctor about what the options might be.✓ Cut yourself some slack. It's normal to have a lot of emotions around this, and it's better not to squish them down. Don't hesitate to lean on someone you love or seek the help of a professional.	<ul style="list-style-type: none">✓ Walk. The world's oldest form of exercise is truly the greatest. Try to fit in +/- 40 minutes of brisk walking per day.✓ Move. If you can't walk or otherwise exercise because of fatigue or an injury, find another way to get off the couch. Movement increases heart rate, which helps deliver nutrient-rich blood to your cells, aiding recovery.✓ Pump some iron. As allowed, a little resistance training will help keep your muscles toned and supportive.	<ul style="list-style-type: none">✓ Eat brightly colored, nutrient-dense foods. You want everything you eat to mean something for your recovery and pack the most “punch.”✓ Skip the fast food and processed meat. One of the things we know for sure is that inflammation and prostate cancer go hand in hand. It's best to entirely eliminate these inflammatory foods.✓ Limit or eliminate refined sugar. Cancer loves sugar. You hate cancer. Do the math: next time you have a craving, grab a piece of fruit instead.



of hormone therapy called relugolix for advanced prostate cancer; see [Types of Hormone Therapy](#) on page 67. Clinical trials show a benefit in patients with more aggressive localized disease who receive hormone therapy with radiation therapy. 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 unfavorable intermediate-risk prostate cancer and nearly all high-risk prostate cancer. It is often given for unfavorable intermediate-risk cancer for 4 to 6 months (called short-term hormone therapy), and for 1.5 to 3 years in men with high-risk localized prostate cancer.

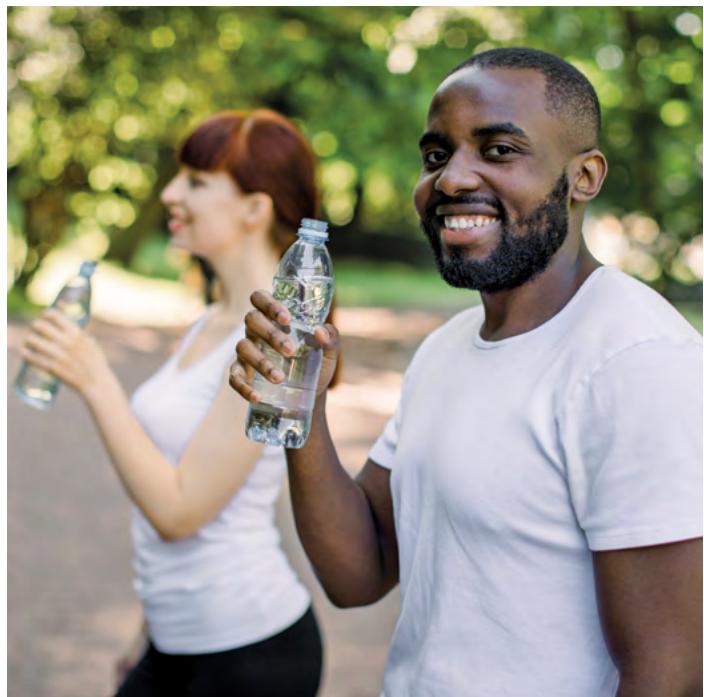
Hormone therapy should not be given to men with low-risk prostate cancer and is not a standalone treatment for localized prostate cancer in any risk category.

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.



Men diagnosed under the age of 50 may be at higher risk for more aggressive disease. See also: Patients Aged 50 and Younger at pcf.org/guides.

EXPERIMENTAL 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.

FOCAL THERAPY

“Focal” therapies are treatments that target just a region of the prostate thought to have the tumor, instead of treating the entire prostate gland. None of these therapies have yet been proven to have the same long-term success as surgery or radiation therapy in large clinical trials, and are still considered investigational treatments.

The likelihood of recurrence is high with focal therapy due to the fact that in over 80% of cases prostate cancer is actually “multi-focal,” meaning even if the biopsy and/or MRI showed the cancer to be in only one area, there is likely tumor in many areas of the prostate. In fact, some studies suggest that more than 30% of prostate cancer tumors are invisible on prostate MRI.

Cryotherapy is also used as a secondary local therapy in men who underwent radiation therapy as initial treatment for localized 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 an 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.

Proton Beam Radiotherapy

Protons are similar to photons (traditional x-ray radiotherapy) in many ways. However, proton beam therapy has not been shown to improve cure rates or quality-of-life outcomes over other forms of radiation therapy, and may actually increase rectal side effects. There have been no completed head-to-head trials comparing proton beam radiotherapy to either surgery or traditional x-ray (photon) beam radiotherapy. Proton beam radiotherapy is often viewed as an experimental or unproven treatment for prostate cancer. Insurance companies often do not cover it (unless you are participating in a research study) and it is typically very expensive.

High Intensity Focused Ultrasound (HIFU)

HIFU is not FDA-approved for the treatment of prostate cancer, and is thus experimental.

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. 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. Serious side effects have also occurred after HIFU, despite it being “focal.”

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.”

Most of the published literature has demonstrated relatively high recurrence rates with HIFU, and we are still learning how best to optimize and deliver this treatment.

Using HIFU to treat only the portions of the prostate thought to be cancerous instead of the entire prostate gland is an area that is being investigated.

Primary Hormone Therapy

Since testosterone serves as the [main fuel for prostate cancer cell growth](#), it is 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. Multiple large studies with very long follow-up have shown that survival is worse with hormone therapy alone compared to 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.



Be an informed patient: investigate all choices that apply to your cancer, compare treatment options and side effects, and discuss decisions with your family as appropriate.

TREATMENT OPTIONS BY STAGE

While each of the therapies listed below is described in detail in other sections of the guide, the following table summarizes the most common treatment options for each specific type of prostate cancer. Talk with your doctor about your disease stage and which option(s) might be right for you.

Local/Locally Advanced			
Low Risk	Favorable Intermediate Risk	Unfavorable Intermediate Risk	High Risk
Active surveillance - OR - In rare cases, surgery or radiation	Radiation or surgery - OR - Active surveillance for select patients	Radiation + short-term ADT - OR - Surgery +/- radiation	Radiation + long-term ADT - OR - Surgery with high probability of radiation +/- ADT
Locally Recurrent			
If Your Initial Treatment was Surgery	If Your Initial Treatment was Radiation ¹		
Radiation +/- ADT	Brachytherapy or SBRT ² or Cryotherapy or Surgery		
Advanced/Metastatic ³			
Rising PSA, No Detectable Tumors, Not on ADT	mHSPC	nmCRPC	mCRPC <i>Talk to Your Doctor About Your Options</i>
Observation - OR - PET imaging to guide metastasis-directed radiotherapy - OR - Selective use of ADT	ADT + radiation to the primary tumor + androgen directed therapy or docetaxel ⁴ - OR - ADT + androgen directed therapy or docetaxel ⁵ - OR - ADT + darolutamide + docetaxel - OR - ADT	Androgen directed therapy + ADT - OR - Observation + ADT for select patients	<ul style="list-style-type: none"> ► Androgen directed therapy ► Taxane chemotherapy ► Sipuleucel-T ► Radium-223 ► Pembrolizumab (if you have specific tumor mutations) ► PARP inhibitor (if you have specific genetic or tumor mutations) ► Platinum chemotherapy ► PSMA radionuclide therapy

¹All +/- ADT.

²Stereotactic body radiation therapy.

³Consider a clinical trial.

⁴For low-volume disease.

⁵For low- or high-volume disease.

Definitions and Where to Find More Information in This Guide

Risk groups: Indicates risk for developing recurrent, aggressive prostate cancer and is based on PSA, DRE, biopsy, and extent of spread (page 33)

Active Surveillance: A strategy to follow low-risk cancer closely so that treatment is deferred to only if and when it is needed (page 35)

Surgery: Removal of the prostate and seminal vesicles; radical prostatectomy (page 37)

Radiation/radiation therapy: The precise killing of cancer cells with ionizing radiation (photons) from outside the body (page 38)

ADT (androgen deprivation therapy or hormone therapy): Medication given to stop testosterone from being produced or to block it from acting on prostate cancer cells (page 66)

Locally recurrent prostate cancer: Your PSA is rising after treatment and your doctor has determined that the site of recurrence is in or near the prostate (page 61)

Brachytherapy: Internal radiation therapy in which radioactive “seeds” are placed inside the prostate (page 40)

Cryotherapy: A less-common approach in which argon gas or liquid nitrogen are used to freeze prostate cells, killing them (page 44)

Advanced/metastatic prostate cancer: Prostate cancer that has spread beyond the region of the prostate (page 66)

mHSPC: metastatic hormone-sensitive prostate cancer (page 69)

nmCRPC: non-metastatic castration-resistant prostate cancer (page 72)

mCRPC: metastatic castration-resistant prostate cancer (page 72)

PET imaging: Newer, more sensitive imaging scans that can be used to detect sites of cancer throughout the body (page 62)

Androgen directed therapy: Newer types of hormone therapy that are used in advanced prostate cancer and may be effective after the cancer no longer responds to ADT (page 71)

Taxane chemotherapy: A type of chemotherapy that kills rapidly dividing prostate cells by disrupting their structures (page 73)

Sipuleucel-T: A therapeutic cancer vaccine: the patient’s own immune cells are taken from the blood, stimulated in a lab, and reinfused (page 74)

Radium-223: A radiopharmaceutical used to treat men with mCRPC and bone metastases (page 76)

Platinum chemotherapy: Not yet FDA-approved for prostate cancer, but may be used when all other options are exhausted (page 73)

Pembrolizumab: An immunotherapy used in patients whose tumors have specific mutations (page 74)

PARP inhibitor: Precision medicine oral medications for men with mCRPC and certain genetic or tumor mutations (page 75)

PSMA radionuclide therapy: Precision medicine for men with mCRPC delivers a small dose of radiation to prostate cancer cells (page 75)

Clinical trial: Used in all stages of prostate cancer to develop life-extending and potentially curative new treatments for patients (page 86)

“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

Mental Health

Your 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.

Just as with your diagnosis, and regardless of which treatment option you choose, you may experience difficult feelings about your situation.

**New feelings about treatment are normal.
Remember, you do not have to face this alone.**

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 prioritize yourself 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 after local treatment are less frequent and severe than they have been historically. 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.

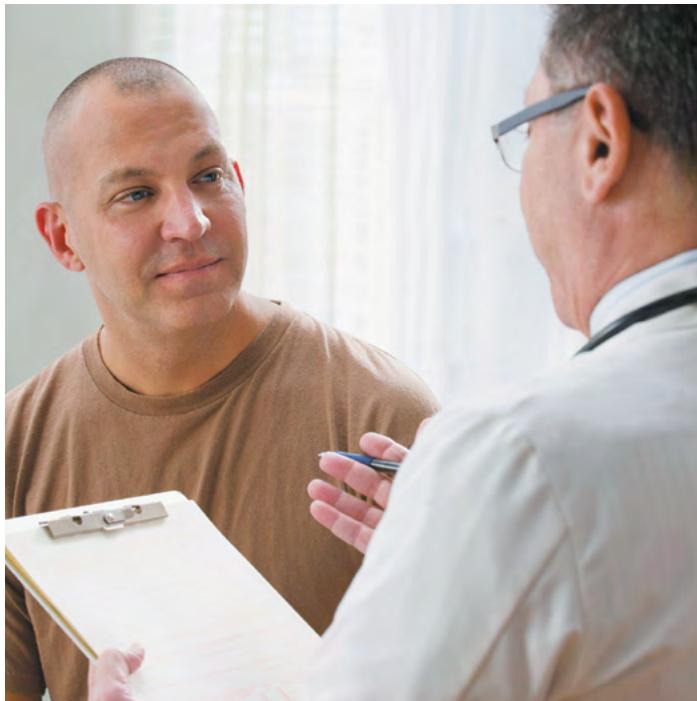
Early management of side effects has been shown to help patients live longer, better lives.

It is extremely important that you communicate with your care team 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.

STATINS

Statins are widely used to lower cholesterol.

Several studies suggest possible benefits to men with prostate cancer. For example, among high-risk prostate cancer patients, men taking statins were 20% less likely to die. More research is needed, but the bottom line is: if you're already on statins, talk to your doctor about staying on them during treatment.



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.

For resources surrounding mental and physical side effects from treatment, Us TOO is a non-profit organization providing local peer-to-peer support groups.

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 3 to 6 months for the first 3 to 5 years, then yearly from that time on. 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](#) (page 59) discusses all of the things that you should know about if this happens.

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 related to advanced or metastatic prostate cancer, see [Side Effects of Treatments for Advanced Prostate Cancer](#) (page 78). Remember, before choosing any treatment, discuss worst-case possibilities of side effects with your doctor.

Prostate cancer grows over years and decades. Consider short and long term quality of life factors when you make treatment decisions.

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, 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 strengthening exercises. The majority of men regain urinary control within a year; approximately 1 in 5 men will have mild leakage requiring the use of one or more pads per day long-term. This rate depends on patient factors (older age and obesity are risk factors for worse urinary incontinence) and surgeon factors (more experienced surgeons typically have better outcomes.) Men over 65 years old are more likely to have urinary incontinence after surgery.

Pelvic floor muscle training (aka “Kegels”) with a physical therapist can help. In the case that incontinence persists past a year, a **urethral sling** or **artificial urinary sphincter** can potentially correct the leakage. Men with obstruction from BPH can expect their urinary stream to improve substantially after surgery.

Radiation therapy is targeted to the prostate. Advanced technology directs the dose of radiation away from the bladder and rectum. The urethra runs through the middle of the prostate, so it will receive radiation, but fortunately, the urethra is very resistant to radiation therapy, and long-term urinary leakage is rare (less than 1 in 100). However, it 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 cause **nocturia**, or waking up more at night to urinate.

Bowel Function

Solid waste that is excreted from the body moves slowly down the intestines, and, under normal circumstances, the resultant stool passes through the rectum and then exits via the 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, but it isn't often used in these types of cases.

Since the rectum sits right behind the prostate, it may also receive some radiation during treatment. With modern **radiation therapy** (IMRT or IGRT), it is very rare to have moderate or severe bowel problems (1%–3%), and with the use of a **rectal spacer** (see below) this rate is reduced to near 0%. During radiation therapy you may experience softer stools.

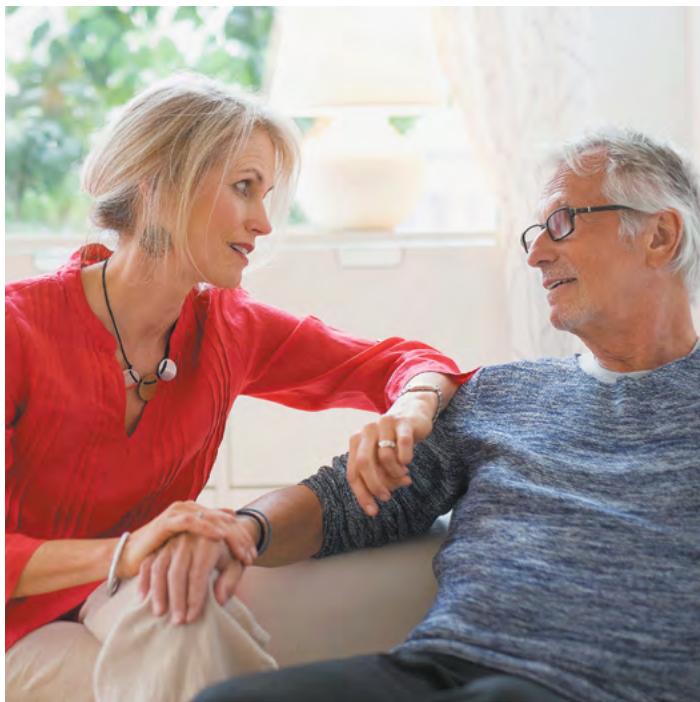
SURGERY VS. RADIATION THERAPY: MORE TO THINK ABOUT

There is no easy or obvious answer when choosing between treatments. Although many patients have good long-term urinary and bowel function after treatment, the truth is that your body wasn't meant to have surgery or radiation therapy, and you may have side effects. In the hands of an expert physician or at a high-volume center, outcomes tend to be better.

In general, surgery is more likely to lead to urinary incontinence and erectile dysfunction early on after treatment. Radiation is more likely to cause urinary frequency, urgency, or nocturia, a greater potential risk of rectal toxicity depending if a rectal spacer or other image-guidance techniques are used, and a later decline in erectile function. Be sure to read this section carefully. Go to pcf.org for lead editor Dr. Dan Spratt's common considerations when choosing a therapy.

These symptoms typically resolve within a few weeks of completing radiation therapy. With modern radiation, only 2% of men will have bothersome rectal bleeding that may occur months or years after treatment, and with a rectal spacer this rate is reduced to less than 1%. 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.

Since 2016, the FDA has approved a new device, called a rectal gel or spacer (SpaceOAR) to further reduce rectal side effects of radiation therapy. In a randomized trial it was shown that the rectal spacer reduces bothersome rectal side effects to 0%. The benefits were more noticeable in long-term follow-up. Ask your physician if they offer SpaceOAR at their practice and if your insurance covers it.



Although some erectile function may be lost in some patients during treatment, many options exist for managing side effects (see inset on page 54).

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. Other less common, treatable side effects that can influence function include scarring in the penis (Peyronie syndrome) and climacturia (releasing a small amount of urine during ejaculation). Fortunately, beyond short-term side effects, there is also room for great optimism: many excellent treatments for managing erectile function (see inset on page 54) exist on the market today.

In fact, within 1 to 2 years after treatment, most men with intact nerves will see a substantial improvement. However, modern studies have shown that overall about 40% of men lose some erectile function after surgery. The skill of your surgeon or physician can have a significant impact on this outcome, so it is very important to select **your team** carefully. Likewise, men with baseline erectile dysfunction and/or other diseases or disorders that impair the 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 maximum 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. Four main components of erectile function may be affected by prostate cancer treatment:

1. Libido (sex drive) is commonly decreased by **hormone therapy** 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 normalizes after completing hormone therapy. Loss of libido can be a major concern for some patients and/or their partners and much less of an issue for others.

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. Fertility is different from erection and orgasm. Orgasm may still occur (without ejaculate) but 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.

Hormone therapy aside, diagnosis and treatment can bring about complex feelings that include sadness, anger, and anxiety. These are normal feelings that, when unmanaged, can likewise compromise your sex drive; don't be shy about seeking individual or couples counseling during treatment.

2. Mechanical ability is the ability to achieve a firm erection. It is controlled by the nerves and vessels that are closely 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, 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. The quantity of 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 minimal or no ejaculate afterwards. So although you may be able to have an erection and reach an orgasm, nothing may come out. Initially, after surgery primarily, you may ejaculate blood, which will improve over time.

Prostatectomy: Since the 1980s, most men with localized disease 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 30%–60% of men who have the ability to have an erection before surgery will maintain this ability 2 years post-surgery. This number varies greatly with surgeon expertise, age, and obesity. In general, men with lower-risk prostate cancer have higher than average rates of erectile function. In contrast, it is more challenging to spare the nerves in high-risk prostate cancer, since the tumor may have invaded more tissue—leading to erectile function rates that are lower than average.

If you receive radiation therapy after surgery, your likelihood of erectile dysfunction will increase, since you are being exposed to the cumulative side effects of both treatments.

Radiation therapy: Similar to surgery, damage to blood vessels and nerves after radiation therapy can result in decreased erectile function. However, the timing of the effects may be different. 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 60%–85% of men who have baseline erectile function before treatment will keep erectile function after treatment. Radiation therapy has delayed effects on erectile function vs. surgery; within 15 years after treatment, the rates are similar to those who underwent surgery.

These rates do not appear to be affected by the use of short-term (4 to 6 months) hormone therapy, but are more likely to 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 90% of men maintaining baseline function. This technique is being tested in an ongoing randomized trial. Ask your radiation oncologist about vessel-sparing radiation therapy.

EVERY PATIENT EXPERIENCE IS UNIQUE

Special topics are available for download at pcf.org/guides:

- ▶ Patients Aged 50 and Younger
- ▶ Additional Topics for Black Men and Their Families
- ▶ Gay/Bisexual Men and Trans Women
- ▶ Your Care During the COVID-19 Pandemic

Management of Erectile Function

Oral medications such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®)—a class of drugs known collectively as **PDE5 inhibitors**—relax the arteries 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.

Alprostadiol (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.

Alprostadiol (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 for this reason the treatment is sometimes used only after other approaches have not worked. However, it is one of the most consistently effective options after prostate cancer treatment.

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 blood flow.

A **surgically inserted penile implant** can be up to 100% effective, and about 90% 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.

WHAT'S ON THE ED TREATMENT HORIZON?

Neuro-protection therapies: We know that trauma to the body can cause tissue damage both in and around the trauma site. Fortunately, with prostate cancer surgery we know when the trauma is going to take place, and we know exactly what tissue area will be affected (unlike, say, in the case of a stroke). Therefore, researchers are looking into what preventative action we can take to strengthen and preserve the nerves around the penis before surgery.

Neuro-modulation therapy: Scientists are also using **regeneration biology**—e.g., using natural tissues like stem cells, umbilical tissues, and growth factors—to deliver protection before during and after surgery. Treatments like these have been successfully used in colorectal cancer and are now being applied to prostate cancer.

REMEMBER: ERECTILE DYSFUNCTION IS NOT A DISEASE STATE. IT'S NOT A DISEASE YOU HAVE GOTTEN. IT'S A SIDE EFFECT THAT CAN BE MANAGED.

Great strides have been made in the field of erectile dysfunction in the last 20-30 years. If you were a prostate cancer patient in the 1980s, your option was to take a single oral medication or get a penile prosthesis. Today, patients and doctors can choose between oral medications, injectable therapies, vacuum devices, penile prostheses, and erection-inducing suppositories.

Today, the name of the game for patients is shared decision-making. In 2018, the American Urological Association released 25 new guidelines for diagnosis and treatment of erectile dysfunction ranging from evaluation to diagnosis and treatment. The recommendations indicate that men should be informed of all options that are not contraindicated (e.g., harmful to their health); previously, some treatments were seen as first-line defense and others as second-line, regardless of the personal goals and characteristics of the patient.

In the recent past, oral medications such as Viagra®, Levitra®, Cialis®, or Stendra® were considered “first line of defense” for treatment. But now we appreciate that some men’s situation may dictate a better starting point. Here are two examples. If you are a man who had nerve-sparing surgery and you were potent before surgery, oral medications may be a great

starting point for you. On the other hand, if you are a man who had compromised erectile function before surgery (for any number of reasons), and your nerves were not spared during surgery, you may opt to start with a mechanical prosthesis. But here’s the thing that might be both frustrating and liberating: there’s no right answer we can give you as to which treatment fits you. It’s important to talk to your urologist to discuss your overall physical and mental health, as well as your ideal lifestyle outcomes. If you are in a long-term relationship, it could be helpful to also involve your sexual partner in these conversations.

If you have yet to go into treatment, make sure to take the SHIM (Sexual Health Inventory for Men) test. Your score from this questionnaire will provide a documented, realistic baseline to which you might return after surgery. It is important to keep in mind that while you might return to this baseline, prostate cancer treatment will never result in better erectile function than you had before. Visit pcf.org/SHM to get your score.

With all that said, remember that one of the issues with all current ED treatments is that they are not curative—they all provide varying degrees of temporary correction to the problem.

Consult your doctor as to which of these options might be right for you. Despite what you may have been told, it is not necessarily the case that all men should start with oral medications. If you are a man with significant vascular disease or limited nerve function, ask your doctor if you should go straight to a pump or injections, which have traditionally been considered “second-line” defenses. Just as the Prostate Cancer Foundation is a strong advocate for precision medicine, we believe in precision lifestyle treatments for men to live a full life after treatment. Make sure to discuss side effects and the pros and cons of each treatment with your doctor. Beware of over-the-counter treatments, supplements, or expensive experimental treatments that promise miraculous results.

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.

There is growing scientific evidence that suggests healthy diet and lifestyle practices may actually slow the growth and progression of prostate cancer. Cutting-edge studies are starting to unpack some unexpected data. For example, research suggests that drinking coffee regularly, 1-2 cups per day, can help prevent aggressive forms of prostate cancer. Another study suggests that the bacteria in your gut, known as your **microbiome**, may in fact alter your immune system's ability to respond well to cancer treatment. To stay up to date on the latest in lifestyle research, subscribe to the newsletter at pcf.org.

Diet

Just a few simple changes in your daily eating habits can help support healthier living as you recover from prostate cancer. These changes may decrease your time to return to normal function, 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. Research is ongoing, but the classic "Mediterranean Diet" is anti-inflammatory and heart-healthy, giving every prostate cancer survivor a better chance to maximize longevity through lifestyle.

1. Vegetables. Incorporate cooked tomatoes (preferably cooked with olive oil) and cruciferous vegetables (like broccoli and cauliflower) into most 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 and Protein. 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. Avoid processed meats (lunch meats) that contain nitrates and 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 brightly-colored vegetables and whole grains, rather than relying on vitamin supplements. (Vitamin D may be the exception). In particular, avoid excessive calcium substitutes. Plant-based sources of calcium include dark green leafy vegetables, soy, and almonds. For more on supplements, see page 88 in *The Science of Living Well, Beyond Cancer* at pcf.org.

Exercise

Exercise is essential for a healthy lifestyle. For prostate cancer survivors, exercise as much as you are physically able, at a pace that matches your personal fitness. More research studies are emerging which indicate that exercise during cancer treatment can improve long-term survival when combined with traditional therapies. Even mild exercise has been proven to both reduce risk of prostate cancer recurrence and improve survival in patients, even in those with advanced forms of disease.

When you exercise, your heart rate goes up, increasing the rate at which nutrient-rich blood circulates through the body. For those who are able to exercise, walk as briskly as you can (3 or more miles per hour), and try to add bouts of more vigorous activity like jogging, swimming, or biking as you are able.

Research suggests that exercise affects energy metabolism, oxidative stress, immunity, and androgen signaling pathways, and is therefore beneficial for men with prostate cancer. Most importantly, exercise reduces levels of inflammation that produce prostate cancer growth. Evidence shows that exercise significantly reduces the risk of prostate cancer recurrence. The key to exercise is consistency: exercise as regularly as you can, most days of the week, and increase the intensity of your exercise as you are able.

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**, so it is never too late to quit. 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. Quitting smoking is also associated with improved penile blood flow and erections.

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 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



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

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.

For more detailed information on nutrition, exercise, rest, and the relationship between obesity and cancer, visit pcf.org to download a free copy of *The Science of Living Well, Beyond Cancer*.



STOP

The next 2 sections are for men with rising PSA levels after initial treatment, or 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 & Grandchildren," a discussion of the genetics of prostate cancer risk.

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

— PATIENT



DETECTING RECURRENCE

If you're reading this chapter, it's because your cancer cells have previously been removed with surgery or killed with radiation, but your PSA has started to rise again.

In some cases, prostate cancer cells might have 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.

PSA monitoring after treatment is an important way of understanding whether or not all the prostate cancer cells have been destroyed. If you previously underwent surgery, your PSA should be undetectable. However, after radiation, since PSA is produced by all prostate cells, not just prostate cancer cells, there may be residual normal (benign) prostate cells that still make some PSA.

If your PSA begins to rise, 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, these imaging tests may not provide enough information to determine a further course of action. Newer **molecular PET imaging scans** can be done at select centers; the imaging agents include C11-choline (performed in limited clinic centers), F18-fluciclovine (Axumin; FDA-approved and available across the U.S.), and F18-sodium fluoride (to evaluate for bone metastases, usually to confirm findings from bone scans). A clinical trial of men with prostate cancer and rising PSA levels after surgery found that cancer control was improved when doctors used F18-fluciclovine PET imaging instead of conventional imaging.

PSMA-PET is the newest molecular imaging technology that is more sensitive in detecting prostate cancer metastases in the body, and was FDA-approved in 2020 (see page 62). If your PSA is less than 0.2, even a PSMA PET scan may not yet be able to pinpoint the location of cancer. A clinical trial comparing PSMA PET to fluciclovine PET for treatment planning is underway.

It's important to note that some of these tests may not be covered by your insurance yet.

Whole body multi-parametric MRI (MP-MRI) is another emerging imaging technology for measuring sites and burden of metastatic disease that may be more sensitive than CT and bone scans. Its effectiveness is currently being tested in clinical trials. To follow these and other evolving technologies, visit pcf.org/newsletter.

UNDERSTANDING THE NUMBERS

After prostatectomy, PSA drops to "undetectable levels," (less than 0.1). This is effectively zero, 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 zero with this treatment. Rather, a different low point is seen in each individual, and that low point, called **nadir**, becomes the benchmark by which to measure a rise in PSA.

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. After radiation, 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 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

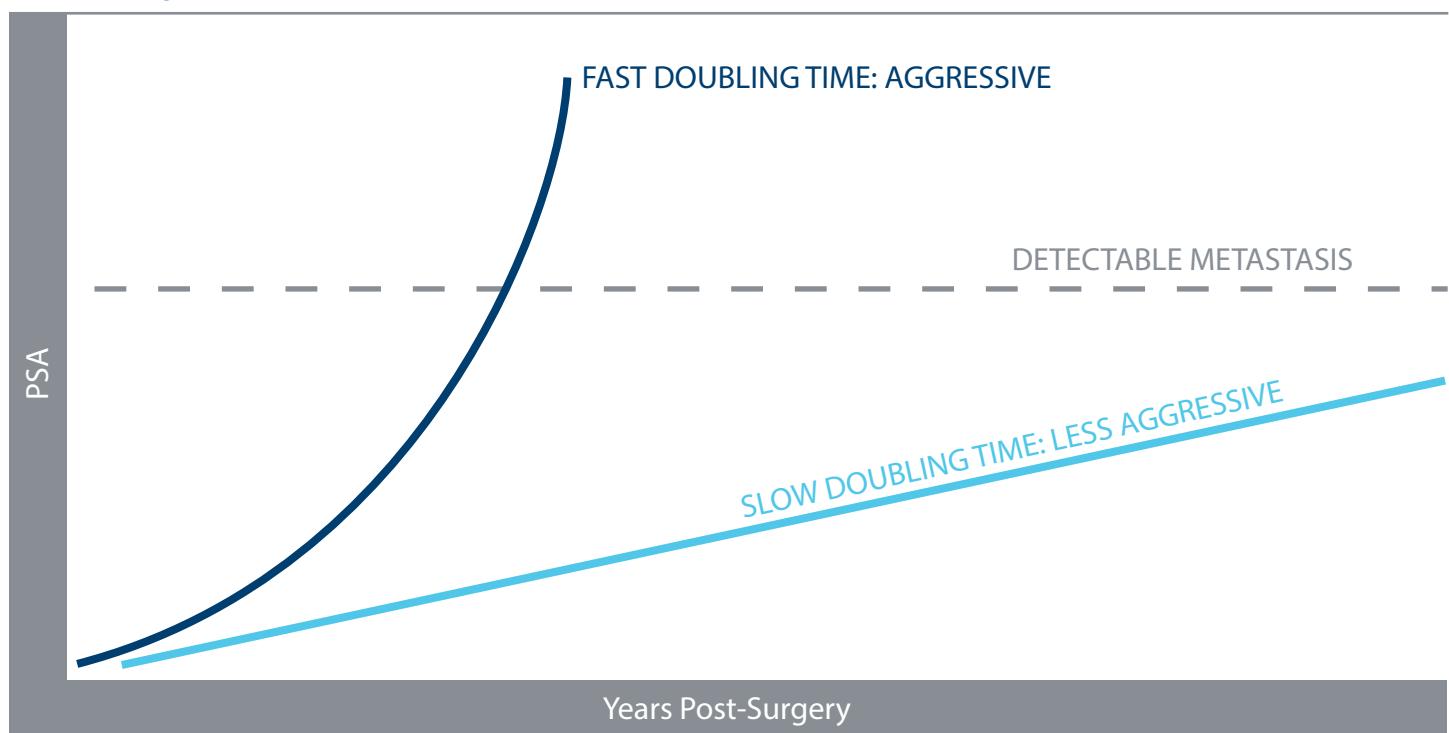
Radiation Patients: if your PSA is 2.0 ng/mL above your lowest reading after treatment (referred to as your “nadir” reading), as measured on 2 consecutive tests

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 a urologist, radiation oncologist, and medical oncologist—to help you decide on the best course of action.

PSA DOUBLING TIME

The rate (or velocity) at which your PSA rises (and how quickly it doubles) 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 Doubling Time



When looking at PSA doubling time 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) 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) had the least aggressive tumors and were less likely to die from their disease.

The faster your PSA rises, the more aggressive your disease is considered.

That said, measuring and using PSA doubling time is not an exact 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 an imaging scan to see if the cancer has spread to my bones or other organs?
- ▶ 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?
- ▶ Should my treatment plan also include androgen directed therapy or docetaxel?
- ▶ 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?

THERAPIES FOR LOCALLY 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 your doctor has determined that the site of disease recurrence after surgery or radiation therapy is **local**, meaning in or near the prostate. In this case, re-treating the prostate region may provide a second chance at cure. This secondary treatment is often referred to as “salvage” therapy.

Whether your initial treatment was radiation or surgery, you can discuss salvage options with your treatment team (see chart opposite).

Salvage Therapy Options After Recurrence

If your initial treatment was <i>surgery</i> , your salvage treatment can be:	If your initial treatment was <i>radiation</i> , your salvage treatment can be:
Radiation	Further radiation with either brachytherapy or SBRT
ADT	Cryotherapy
	Surgery
	ADT

As with any secondary form of treatment, there is the risk of increased side effects beyond the initial treatment. While salvage brachytherapy, cryotherapy, and salvage prostatectomy appear to have similar rates of efficacy, salvage prostatectomy appears to carry the greatest risks of side effects, including urinary incontinence, rectal injury, and impotence, and should only be attempted at high-volume academic medical centers.

(continues on page 64)

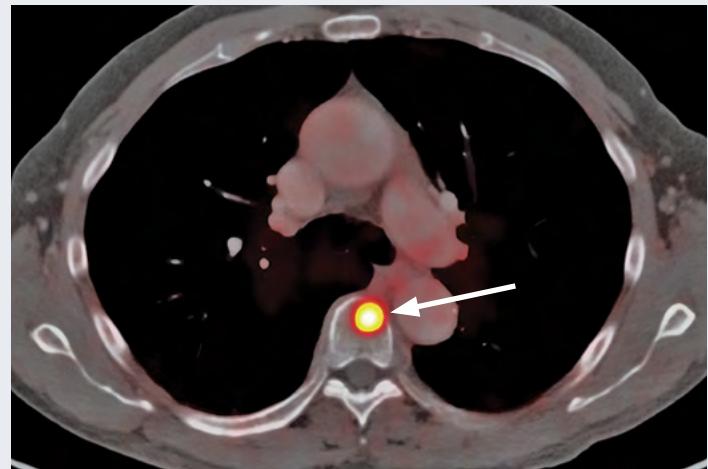
SPECIAL FEATURE: PSMA PET IMAGING

In December 2020, the FDA first approved a new type of scan, PSMA PET, to find prostate cancer throughout the body. This more sensitive scan can detect prostate cancer metastases much earlier, when they are much smaller, and can show the specific location of these very tiny amounts of cancer anywhere in the body. This is an incredibly important development for men with metastatic disease as well as any man worried about rising PSA.

PSMA PET imaging is approved for two types of patients: 1) patients with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy (for example, patients newly diagnosed with high-risk prostate cancer), and 2) patients who had prostate cancer and were previously treated (i.e., with radiation or surgery) and now have a suspected recurrence, based on elevated PSA levels. This information will help doctors make decisions in caring for patients with prostate cancer.

Compared to conventional scans used for prostate cancer detection, such as CT, bone scans, and MRI, PSMA PET is over twice as sensitive and can detect metastatic prostate tumors the size of a small garden pea or a BB pellet.

How does it work? PSMA, short for Prostate Specific Membrane Antigen, is a protein that is found on the surface of prostate cancer cells. Researchers use a small chemical that binds to PSMA, honing in on prostate cancer cells wherever they are in the body. Attached to this binding chemical is a radioactive "reporter." Patients are given a one-time injection of this combination molecule into the bloodstream. They then pass through the imaging camera (PET/CT or PET/MRI scanner) that "lights up" areas where the molecule has accumulated – i.e., sites of prostate cancer (see photo).



PSMA Imaging. A traditional CT scan (left) does not clearly show metastasis in the spine. In the "fused" PSMA PET/CT image (right), the prostate cancer metastasis "lights up."

Currently, there are two types of PSMA PET imaging agents that are FDA-approved: ¹⁸F-DCFPyL (PYLARIFY®) and ⁶⁸Ga-PSMA-11 (Locametz® and Illuccix®). Availability varies across the U.S. If you and your doctor are considering a PSMA PET scan as part of your care, ask which type might be right for you and how you can access it. Check with your health insurance provider to avoid any unexpected out-of-pocket costs.

PCF has invested in developing this unique PSMA scan for decades (no other cancer can boast such specific, targeted imaging yet). PCF funding was critical to the development of ¹⁸F-DCFPyL, and approval of ⁶⁸Ga-PSMA-11 was based on studies led by PCF-funded investigators. Research is ongoing to better establish how PSMA PET imaging will best benefit certain prostate cancer patient groups.

The radioactive molecule is very safe, and no side effects have been reported among hundreds of thousands of patients in clinical trials. The amount of radiation you are exposed to from a PSMA-PET/CT scan was found to be lower than with current standard-of-care imaging techniques.

In March, 2022, PSMA-based technology was approved not just to see cancer, but to deliver targeted treatment. ¹⁷⁷Lutetium-PSMA-617 (Pluvitco®) was approved by the FDA for certain patients with advanced prostate cancer. For more details on the use of PSMA in the treatment of prostate cancer, see PSMA Radionuclide Therapy on page 75.

A team of PCF-funded investigators including (from top) Thomas Hope, MD, at UCSF; Johannes Czernin, MD; and Jeremie Calais, MD, MSc, at UCLA led the development of ⁶⁸Ga-PSMA-11.

Researchers continue to study how PSMA PET can be best used to improve care for patients with prostate cancer.



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.

The next sections provide more detail on methods of salvage treatment for local recurrence.

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 of killing any remaining prostate cancer cells that have been left behind. Approximately 80% of men who have a rising PSA after surgery have residual 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.

TIMING OF SALVAGE RADIATION AND USE OF HORMONE THERAPY

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 whose PSA has risen above 0.6 ng/mL, hormone therapy is usually added to salvage radiation therapy, which has been shown to improve the cure rate. For men with a low PSA (0.6 ng/mL or less) at the time of recurrence, addition of hormone therapy is usually not needed.

The side effects that you suffer from salvage radiation therapy are directly related to the amount of side effects suffered from the surgery. For example, if you already have some degree of urinary incontinence or poor erectile function, salvage radiation therapy has the potential to worsen these to a more noticeable degree.

If you are considering salvage treatment, discuss your options and the risk and benefit trade-offs carefully with your treatment team.

In general, all salvage therapy therapies are more likely to cause side effects than the primary therapy, since the side effects are additive. These include rectal bleeding, incontinence (urinary leakage), strictures and difficulty urinating, diarrhea, and fatigue. Importantly, rectal spacers are not used after surgery, and thus rectal side effects with post-operative radiotherapy may be slightly higher than radiotherapy upfront. Be sure to discuss potential side effects with your doctors before deciding on a course of therapy, but don't delay; side effects may be better than risking disease spread. In some cases, hormone therapy might be given in conjunction with radiation treatment, so it is also important to discuss the impact.

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.

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. Be sure to carefully weigh all of the different factors that can play a role in determining whether this approach is right for you. Recent evidence suggests that salvage prostatectomy has higher rates of side effects than other similarly effective therapies discussed below. An estimated 1 in 5 men will experience a severe side effect after salvage surgery, compared to around 1 in 10 with salvage brachytherapy or SBRT.

Brachytherapy Following External Beam Radiation

The use of radioactive seed implantation or high-dose-rate brachytherapy using catheters after EBRT has 5-year disease-free rates of around 60% (very similar to the success of salvage radiation therapy after surgery). Side effects from brachytherapy following external beam radiation can sometimes be less frequent and less severe than other therapies, such as salvage prostatectomy. 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.

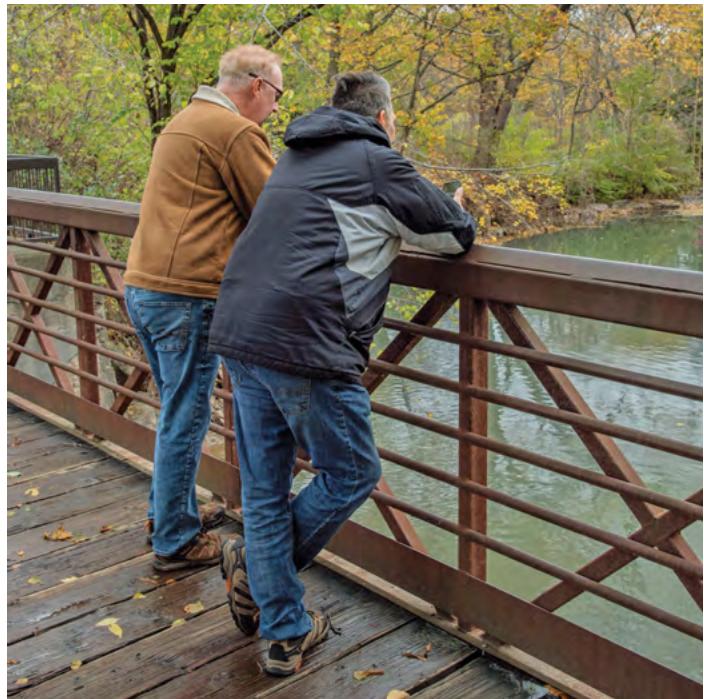
SBRT Following Radiation

Stereotactic body radiation therapy ([SBRT](#)) is sometimes used as a secondary local therapy in men who previously had radiotherapy. The old dogma of “Once you have had radiation you cannot have it again” is no longer true. Recent evidence suggests that salvage SBRT has a similar efficacy and side effect profile to salvage brachytherapy, but brachytherapy has more evidence to support its use at this time.

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%-50%. However, because the procedure does not completely destroy all remaining prostate cells, PSA generally does not drop to zero, 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 of 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.



When dealing with recurrence, there is a lot of new information to remember and process. It may be helpful to enlist a friend or family member to act as a health advocate, to help you keep it all straight.

Hormone Therapy Following Radiation or Surgery

In select men who undergo surgery or radiation therapy, the best salvage treatment option may not be more local therapy, but rather hormonal therapy, which is a systemic therapy and therefore acts on tumor sites throughout the body. This is a controversial topic, as most guidelines recommend not giving hormone therapy just for a rising PSA. However, for patients with a rapidly rising PSA or a fast PSA doubling time, some will consider starting ADT. This has been shown to be beneficial especially in men who have lymph node involvement that was found at time of surgery.

Hormone therapy alone, however, is not curative, and is associated with numerous side effects, and thus you should discuss with your physician if this is the right treatment for you. The next section provides more information on hormone therapy and other treatment options for advanced disease.

THERAPIES FOR ADVANCED AND METASTATIC PROSTATE CANCER

In some cases, even in patients who have completed initial or secondary treatment for prostate cancer, the disease recurs again and additional treatment is needed. In other cases, a man may present with **metastatic prostate cancer** (i.e., disease that has spread beyond the prostate) at the time of diagnosis. This section covers treatments for advanced cancers that fall into these two categories.

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

Why Does Prostate Cancer Come Back?

Initially, growth of recurrent or metastatic prostate cancer may stop or slow down in a low-testosterone environment. That's why **hormone therapy** (also called **androgen deprivation therapy** or **ADT**) is usually a part of most treatment plans for advanced and metastatic prostate cancer. Standard ADT is designed to stop testosterone from being produced or directly block it from acting on prostate cancer cells. It is, essentially, "anti-hormone therapy." The majority of prostate cancer cells will stop growing following the removal of testosterone, and many will die. Prostate cancer that can be controlled by standard ADT is referred to as **hormone-sensitive prostate cancer (HSPC)** or **castration-sensitive prostate cancer**.

However, in many men, some prostate cancer cells eventually gain the ability to grow in the low-testosterone environment created by ADT. As these hormone-therapy-resistant prostate cancer cells continue to grow, standard ADT has less and less of an effect on stopping the growth of the tumor over time. Prostate cancer that can no longer be effectively controlled by standard ADT is 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.

The next sections describe treatment options for men with cancer that DOES respond to treatment with hormone therapy (hormone-sensitive prostate cancer, page 66) and cancer that DOES NOT respond to treatment with hormone therapy (**castration-resistant prostate cancer**, page 70).

There are a lot of options described in the following sections that may seem overwhelming at first. But they represent a lot of hope: as prostate cancer gets smarter, research gets smarter too. Advances in science are providing more precise treatments to match your particular form of prostate cancer. For advanced disease, the standard of care—well established, scientifically proven treatment protocols—now includes multiple strategies.

HORMONE-SENSITIVE PROSTATE CANCER TREATMENT OPTIONS

About Hormone Therapy

The timing of when to start 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 hormone 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. 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.

Until recently, the standard-of-care first-line treatment for all patients with hormone-sensitive metastatic disease was ADT alone. However, advances in medical research have generated additional options, making "combination therapy" the standard of care now. Clinical trials have found better survival rates when an approved androgen directed therapy (a stronger form of hormone therapy, discussed on page 68) or docetaxel chemotherapy are combined with ADT. For patients with a low volume of metastatic disease at diagnosis, guidelines now recommend that treatment with

radiation therapy to the primary tumor be considered in addition to ADT. (See [Treating Metastatic Hormone-Sensitive Prostate Cancer](#) on page 69.) It is important to discuss these treatment options with your doctor to determine which choice is right for you.

Types of Hormone Therapy

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. 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 is an option for men who prefer a low-cost, one-time procedure. It also may have a lower risk of cardiovascular complications and fractures compared with drug-based hormone therapy. Because it's permanent and irreversible (essentially, surgical castration), most men opt for chemical therapy instead.

LHRH Agonist: One of the most common hormone therapies in prostate cancer involves blocking the release of LHRH through the use of agonists (substances that initiate a response). LHRH, or luteinizing-hormone releasing hormone (also called GnRH, or gonadotropin-releasing hormone), is one of the key hormones released by the body that initiates the production of testosterone. 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 the first treatment. This can result in a variety of symptoms, ranging from bone pain to urinary issues. Fortunately, this can be prevented by co-treatment with a class of drugs called anti-androgens.

LHRH Antagonists: These are a 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 an injection given monthly to men as an alternative to orchiectomy or LHRH agonists.

WHAT DOES “STANDARD OF CARE” MEAN?

When doctors refer to the standard of care, they generally mean the most widely accepted, approved, and effective treatment protocol for a particular disease state. To reach this level, a new treatment must be supported by high-quality scientific evidence: tested against the existing “best” treatment in randomized clinical trials, reviewed by experts, published in scientific journals, and, in the U.S., approved by the FDA. It is important to understand how this term applies in prostate cancer.

First of all, standard of care does not mean that there is a single best treatment option; for example, in localized prostate cancer, treatment options can include active surveillance, surgery, and radiation. Second, different standards of care apply to different stages and types of prostate cancer, and these constantly improve as we advance research. Thanks to more than 25 years of research funded by the Prostate Cancer Foundation, we have been able to classify and develop treatments for many types of prostate cancer... and sometimes more subtypes within those!

That means it's critical to know and understand what type of prostate cancer you have (e.g., stage, risk level, features of the tumor based on biomarker testing) so that you can understand the relevant standard(s) of care.

Additionally, in the event that a particular treatment is unsuccessful for your type of cancer, you can ask your doctor what clinical trials of investigational treatments might already be underway for which you may be eligible. Clinical trials are vital to improving the standard of care.

Everything described in this guide is standard of care, with the exception of the emerging therapies in Chapter 6.

A new, oral form of LHRH antagonist (relugolix) was approved by the FDA in late 2020. Relugolix has the most rapid suppression of testosterone as well as the fastest recovery of testosterone after stopping ADT. Another advantage is that concurrent anti-androgens to avoid a testosterone flare are not needed. Furthermore, there is growing evidence from multiple studies that LHRH antagonists may result in fewer cardiovascular side effects compared with LHRH agonists.

Orchiectomy, LHRH agonists, and LHRH antagonists are the standard types of ADT. None of these approaches is considered better than the others in terms of cancer control. Your choice may depend on lifestyle factors, schedule, cost, and other health conditions. Anti-androgens, discussed below, are types of hormonal therapy that are used in combination with standard ADT. They work through different mechanisms and are not considered “traditional” ADT.

Anti-Androgens: Anti-androgens such as bicalutamide (Casodex®), flutamide (Eulexin®), and nilutamide (Nilandron®) can help block the action of testosterone in prostate cancer cells. This class of drugs is added to some hormone injections to prevent a temporary rise in testosterone. 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. Of note, gynecomastia (formation/growth of breast tissue) 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 treatment team.

Use of these “first-generation” anti-androgens alone is typically not recommended and has been shown in two clinical trials to increase the risk of death from non-prostate cancer causes, likely linked to cardiovascular side effects.

Medications to Know

Standard ADT	Anti-androgens	Androgen Directed Therapies
<p><i>Lower testosterone levels</i></p> <ul style="list-style-type: none"> ▶ Orchiectomy (surgical castration) ▶ LHRH agonists (e.g., leuprolide) ▶ LHRH antagonists (degarelix, relugolix) 	<p><i>Help block the action of testosterone</i></p> <p>Include:</p> <ul style="list-style-type: none"> ▶ Bicalutamide ▶ Flutamide ▶ Nilutamide 	<p><i>Newer medications approved for men with certain states of advanced prostate cancer</i></p> <ul style="list-style-type: none"> ▶ Abiraterone ▶ Apalutamide ▶ Enzalutamide ▶ Darolutamide

Androgen Directed Therapies: Beginning in 2011, a handful of new “second-generation” hormone treatments began gaining FDA approval for men with certain states of advanced prostate cancer. These are referred to as **androgen directed therapies**. Apalutamide, enzalutamide, and abiraterone are approved for use in combination with ADT in patients with metastatic hormone-sensitive prostate cancer (mHSPC), as well as other clinical states. Darolutamide is an additional drug in this class that initially gained FDA approval in 2019 for the specific clinical state of non-metastatic castration-resistant prostate cancer (nmCRPC). (See also [FDA-Approved Androgen Directed Therapies](#) on page 71.) Each of these treatments is associated with a unique set of side effects.

INTERACTION EFFECTS

Many plant-based supplements have estrogen-like properties and can interact with your medications for prostate cancer or other conditions. Be sure that your doctor has a complete list of all medicines—including any “non-traditional” ones—that you are taking, in order to better monitor their effects on your therapy or the progression of your disease.

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 common is to give LHRH agonists intermittently, meaning that the drug is taken during “on” periods and skipped during “off” periods.

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 response to and tolerability of hormone therapy.

Treating Metastatic HSPC

The previous sections presented background information on the various types of hormone therapy. The next section discusses how they are used, often in combination with other treatments, in metastatic hormone-sensitive prostate cancer (mHSPC). This refers to cancer that has spread outside of the prostate itself, but responds to hormone therapy. “Responsive” and “sensitive” both mean that tumor growth is affected by one of the hormone therapies on page 67. This includes men whose cancer has recurred after prior surgery or radiation as well as men who were initially diagnosed with disease that was already metastatic.

Previously, androgen directed therapies (such as abiraterone and enzalutamide), as well as taxane chemotherapy, had been applied only after cancer becomes metastatic and resistant to hormone therapy (see [Hormone-Resistant Prostate Cancer Treatment Options](#) on page 70 for more information). However, clinical trials then found that for men with mHSPC, adding an androgen directed therapy or docetaxel chemotherapy together with ADT significantly extended survival and length of time before disease progression.

While ADT alone might still be the best choice for some patients, it is now recommended that patients with mHSPC should strongly consider combination therapy with ADT. These options are discussed below.



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

ADT plus androgen directed therapies: In 2018, abiraterone plus low-dose prednisone became FDA-approved for high-risk mHSPC patients who are initiating treatment with ADT. This approval was based on two large clinical trials showing that men on the abiraterone/prednisone/ADT regimen lived longer on average than those taking ADT alone. Ask your doctor to discuss this approach with you if you are starting hormonal therapy for the first time. In 2019, results from 3 large phase 3 clinical trials demonstrated that the addition of apalutamide or enzalutamide to ADT similarly helps men with mHSPC live longer, leading to the FDA approval of both drugs later that year.

In 2022, a “triplet” regimen of ADT plus darolutamide plus docetaxel was FDA-approved for mHSPC. This approval provides further support to the growing evidence for “intensified” therapy of mHSPC.



New life-saving and life-extending therapies are constantly being tested and approved through clinical trials. Visit pcf.org and subscribe for the latest medical updates.

ADT plus taxane chemotherapy: Two large randomized phase 3 trials have demonstrated that, for men with mHSPC, the addition of docetaxel extended overall survival in patients starting hormone therapy. For men with a high burden of metastatic disease, there is stronger evidence for benefit when docetaxel is added to ADT. It is possible that some men with a low burden of metastatic disease may also benefit. Please discuss with your doctor.

ADT plus radiation therapy: For patients with a low volume of metastatic disease at diagnosis, who have not previously received ADT, guidelines now recommend that radiation therapy to the primary tumor (the prostate) be considered in addition to ADT. This recommendation is based on a clinical trial where men with low burden of disease survived longer on radiation + ADT vs. ADT alone. This benefit was not seen among

men with a high disease burden at diagnosis. Ongoing studies are evaluating the benefit of radiation treatment of not only the prostate, but also the metastases in men with “oligometastatic” disease, or having 5 or fewer metastatic tumors.

So how should men with mHSPC choose a treatment plan? Whether to add one of these treatments to an ADT regimen, and which treatment to add, will be based on clinical factors, such as whether the cancer is high-risk, and whether there is a high or low volume of metastatic disease. Talk to your doctor about whether radiation, an androgen directed therapy, and/or docetaxel may be options for you. Intensified treatment (beyond ADT alone) is now standard of care.

Possible benefits, risks, side effects, costs and other issues should also be considered with your doctor. For instance, patients who are older or less healthy may not be able to tolerate docetaxel; in these cases, androgen directed therapies may be the only viable choice. On the other hand, those who can tolerate docetaxel may want to consider it, as the treatment is far less expensive and shorter (6 treatments given every 3 weeks for docetaxel, versus daily treatment until disease progression for the androgen directed drugs).

HORMONE-RESISTANT PROSTATE CANCER TREATMENT OPTIONS

After a few years, prostate cancer cells often evolve ways to thrive despite the low-androgen environment produced by hormone therapy. When this happens, it is called “hormone-resistant” or “castration-resistant.” For instance, tumors may evolve to produce their own androgens or make more androgen receptors. In these cases, because prostate cancer cells still rely on androgens to survive and grow, a number of “secondary” hormone therapy approaches can be used to keep the tumor from growing.

The treatment landscape for castration-resistant prostate cancer (CRPC) is rapidly improving. Treatments

FDA-APPROVED ANDROGEN DIRECTED THERAPIES

In 2011, a new approach to treating advanced prostate cancer was introduced. Abiraterone became the first next-generation androgen directed therapy to gain FDA approval for metastatic castration-resistant prostate cancer (mCRPC). These agents are approved in different settings of advanced disease: metastatic hormone-sensitive prostate cancer (mHSPC), non-metastatic castration-resistant prostate cancer (nmCRPC), and mCRPC. All are taken orally.

Abiraterone (Zytiga®, Yonsa®) works by blocking 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 effects of abiraterone on other steroid pathways. Zytiga is approved for mHSPC in combination with ADT, and for mCRPC. Yonsa is a newer formulation of abiraterone that was FDA-approved in 2018 for the treatment of mCRPC.

Enzalutamide (Xtandi®), apalutamide (Erleada®), and darolutamide (Nubeqa®) act by blocking the activation of the androgen receptor by testosterone. Enzalutamide is approved for mHSPC and for CRPC in combination with ADT. Apalutamide is FDA-approved for the treatment of mHSPC and for nmCRPC, in combination with ADT. Darolutamide is FDA-approved for nmCRPC in combination with ADT and, most recently for mHSPC in combination with docetaxel and ADT. See sections on disease states for more details and [Side Effects of Androgen Directed Therapies](#) for information on possible side effects.

that were previously given to patients only after ADT had begun to fail are now being given upfront, at the time of ADT initiation. Thus, as you read the following sections, please keep in mind that optimal treatment choices are dependent on what treatments have previously been prescribed, and are best discussed with your doctor.

For men on ADT who were using bicalutamide in combination with an LHRH agonist or antagonist, stopping the bicalutamide is the most common first step in secondary hormone therapy. Between 10%–30% of men will respond to anti-androgen withdrawal, which lasts on average 3 to 5 months. However, inevitably, additional therapies will need to be added even if this withdrawal response occurs. Continuing the LHRH agonist or antagonist and adding a new therapy in combination can improve survival and maintain or improve quality of life.

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 ADT alone is no longer an option and other treatment options should be considered, including: 1) more potent androgen directed therapies (which when added to standard ADT are even more effective at blocking androgen activity), 2) non-hormonal therapy options, and 3) emerging near-term therapies. Note that throughout this section, we use the term castration-resistant prostate cancer (CRPC).



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

In 2019, darolutamide also gained FDA approval for the treatment of nmCRPC (in addition to ADT).

Enzalutamide, apalutamide, or darolutamide plus ADT in nmCRPC appear to be about equally effective in clinical trials; which therapy to choose may be based on other factors, including the side effect profiles. If you are a man with rising PSA levels and negative CT or bone scans, talk to your doctor about whether one of these drugs may be right for you. In some cases, monitoring the PSA while continuing ADT may be an option for men at low risk of developing metastatic disease.

Treating Metastatic CRPC

Metastatic castration-resistant prostate cancer (mCRPC) is a clinical state in which men who have previously received hormone therapy see their tumors begin to grow, and sites of metastatic disease can be found on imaging scans.

Androgen Directed Therapies: Abiraterone and enzalutamide are currently approved for the treatment of mCRPC. As these two drugs have similar survival benefits, your doctor will help you pick based on side effects and your other medical issues. For example, enzalutamide is preferred if a patient has diabetes, 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 the choice.

When one androgen directed therapy 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 the best 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. There are blood tests available which determine the presence of a biomarker called AR-V7, and can sometimes be used to indicate whether a patient is more likely to benefit from an androgen directed therapy (abiraterone or enzalutamide) versus docetaxel chemotherapy.

Treating Non-Metastatic CRPC

Non-metastatic CRPC (nmCRPC) is a clinical state in which men receiving ADT begin to see their PSA levels rise (indicating the cancer is developing resistance to ADT), but the sites of cancer are not yet apparent on CT or bone scans.

Prior to 2018, there were no FDA-approved combination treatments for nmCRPC, and these patients typically continued to receive ADT alone, despite evidence of a diminishing benefit. Today, thanks to research funded by the Prostate Cancer Foundation, men with nmCRPC have three treatment options to add to ongoing treatment with LHRH agonist or antagonist therapy which significantly delay metastatic disease and prolong overall survival.

In 2018, the FDA approved two drugs for use in men with nmCRPC: apalutamide and enzalutamide, both of which are taken in addition to continuing ADT.

NON-HORMONAL TREATMENT OPTIONS FOR mCRPC

Most of the treatments previously discussed work by interfering with the androgen pathway. There are several other treatments for metastatic castration-resistant prostate cancer (mCRPC) that block prostate cancer through other types of mechanisms. The therapies described in this section are typically used in patients whose cancer has progressed even after treatment with hormonal therapy (ADT); they are an add-on to ADT. Additionally, ongoing clinical trials are testing whether it may be useful to introduce each of these treatments even earlier in the course of disease progression.

Research is ongoing to find which treatment may be right for each patient, and the optimal sequence of treatments for mCRPC.

Taxane Chemotherapy

Taxane chemotherapy, given with prednisone, is a standard of care option for men with mCRPC. 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 for patients who have a high burden of metastatic cancer as of the first time they start hormone therapy. Taxanes kill rapidly-dividing prostate cancer cells by disrupting the protein structures required for cells to divide.

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

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 any potential concerns about chemotherapy's "bad reputation." Docetaxel can extend life, reduce pain, and improve quality of life. 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. In patients with mCRPC who have progressed on treatment with docetaxel and an androgen directed therapy (abiraterone or enzalutamide), cabazitaxel has been shown to increase time to cancer progression and overall survival compared with taking a different androgen directed therapy (abiraterone or enzalutamide, whichever was not used previously).

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 yet 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 certain genetic 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.

Results from a phase 2 clinical trial have demonstrated that in a subset of patients with very aggressive and atypical cancer features (termed "aggressive variant prostate cancer," AVPC), the addition of carboplatin to taxane chemotherapy may be of benefit.

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 mCRPC. 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. Some data suggest that the greatest benefit from sipuleucel-T is realized when it is used early (i.e., at a lower PSA level).

The treatment process involves drawing blood, 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 typically 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 more 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 is 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), exhibit microsatellite instability (MSI) in the tumor and/or have a high tumor mutational burden (TMB-H). Patients who qualify for this therapy must have progressed on prior treatment and have no satisfactory alternative treatment options. That means pembrolizumab would typically only be considered after other available effective treatments (such as sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223, etc.) have been used or deemed inappropriate.

Studies suggest that about 3%–5% of metastatic prostate cancer patients have evidence of MMR mutations, MSI, and/or TMB-H 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, MSI, and TMB are identified by biomarker 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.

PARP Inhibitors

In May 2020, olaparib (Lynparza[®]) and rucaparib (Rubraca[®]), two medications in a class of drugs called PARP inhibitors, were approved by the FDA for patients with mCRPC whose cancer has progressed despite other treatments and who have mutations in certain genes. PARP inhibitors are a class of precision medicine treatments that were already approved for use in breast and ovarian cancers with mutations in genes that repair damaged DNA. These “DNA damage repair” (DDR) genes include the prostate, breast, and ovarian cancer risk genes BRCA1 and BRCA2.

A sizable proportion of men with metastatic prostate cancer have these mutations and thus may be candidates for treatment with PARP inhibitors: a PCF-funded team discovered that 25%–30% have these mutations in their tumor tissue, and about 12% have inherited DDR mutations in the DNA they got from their parents. Cancer cells that already have mutations in BRCA1, BRCA2, or other DDR genes will instead rely on the repair protein called PARP; blocking PARP with a medication makes the cancer cells unable to repair themselves, killing them.

In practice, not all patients will respond to these medications, and response may be linked to the specific type of DDR mutation. Screening of mCRPC patients to identify those who have DDR mutations and may benefit from PARP inhibitors is now becoming standard of care.

If you have a family history of prostate, breast, ovarian, pancreatic or other cancers, it is important to talk to your doctor about genetic counseling and testing, for you and family members.

Men with metastatic prostate cancer should strongly consider genetic counseling and genetic testing for inherited mutations, as inherited DDR mutations may have treatment implications, and may be associated with an increased risk of other cancers. In addition, this information may be critically important for blood relatives, because they may also have inherited the same cancer risk gene mutation. See also the section on Prostate Cancer Genes in Families on page 91.



30 years ago, metastatic prostate cancer was a death sentence. Today, many options are available, both as standard of care and in the form of clinical trials.

Common side effects of PARP inhibitors include fatigue, nausea, vomiting, diarrhea, decreased appetite, rash, constipation, vomiting, and diarrhea. However, there are some potentially serious side effects, including bone marrow problems, lung inflammation (pneumonitis), and blood clots.

PSMA Radionuclide Therapy

PSMA, prostate membrane-specific antigen, is a protein that is found at high levels on the surface of prostate and prostate cancer cells. 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 using PSMA to target the cancer. ¹⁷⁷Lu-PSMA-617 (Pluvitco[®]) was FDA-approved in 2022 for patients with mCRPC who have received other treatments (androgen directed therapy and taxane-based chemotherapy). Patients must also have a positive PSMA PET scan. Ask your doctor which type of PSMA scan might be right for you.



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

Approval was based on the large Phase 3 VISION trial, which showed that ¹⁷⁷Lu-PSMA-617 prolongs life, reduces disease progression, and maintains quality of life. Studies are underway to test the effectiveness of ¹⁷⁷Lu-PSMA-617 in earlier stages of prostate cancer, and in combination with other treatments such as immunotherapy.

Common side effects of ¹⁷⁷Lu-PSMA-617 include fatigue, dry mouth, nausea, decreased appetite, constipation, and diarrhea. There are some potentially serious side effects, including bone marrow problems and kidney problems. Ask your doctor about precautions to take following radiation exposure.

Radium-223

Radium-223 (Xofigo®) is a radiopharmaceutical chemically similar to calcium that is used to treat men with castration-resistant prostate cancer that has metastasized to the bones. Because of its calcium-like chemical properties, radium-223 is absorbed in areas where bone is actively growing and healing, in place of calcium, the mineral

that would typically be absorbed in these areas of bone to build and repair them. Radium-223 is more likely to be taken up in places where the bone is damaged and is undergoing repair, particularly sites of growing metastases.

Treatment with radium-223 both prolongs survival and improves quality of life, with more time free of the debilitating complications of advanced prostate cancer (such as pain, 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 (e.g., enzalutamide, chemotherapy, abiraterone). This is likely because men with more advanced disease often have cancer that has spread beyond the bones by that time. Radium-223 is delivered intravenously once every 4 weeks. The most common side effects are nausea, vomiting, diarrhea, and swelling of the lower legs and hands (peripheral edema). Your white and red blood cells and platelet counts may temporarily decrease as well.

Guidelines do not recommend that radium-223 be used simultaneously in combination with abiraterone acetate and prednisone/prednisolone or enzalutamide outside of a clinical trial, as this combination was associated with an increased risk for bone fractures. If these medications are given in combination, patients should receive a medication to improve bone density to prevent fractures, such as zoledronic acid or denosumab. A recent study indicated that the risk of fracture is almost entirely eliminated when a bone health agent is added to the combination therapy regime of radium-223 and enzalutamide.

Because no trial has demonstrated a survival benefit from using the two treatments together, concurrent use is generally not recommended outside of a clinical trial. You should talk with your doctor about whether you should also receive a bone health agent when you are starting treatment with radium-223.

Current Treatment Options for Advanced Prostate Cancer

Disease Stage	Treatments to Consider Once This Stage is Reached
Rising PSA but no detectable tumors on imaging <i>No previous hormone therapy or use of radiotherapy after surgery</i>	<ul style="list-style-type: none"> ▶ The standard of care is salvage radiotherapy with or without hormone therapy ▶ Alternative option for patients with a slow PSA doubling time and/or limited life expectancy: surveillance
Hormone-sensitive metastatic disease <i>Cancer has spread outside the prostate and is responsive to hormone therapy</i>	<ul style="list-style-type: none"> ▶ Hormone therapy alone (for select patients) ▶ Hormone therapy + radiation to prostate (newly diagnosed and with low-volume metastatic disease) +/- androgen directed therapy* or docetaxel ▶ Hormone therapy + (androgen directed therapy* or docetaxel) ▶ Hormone therapy + darolutamide + docetaxel
Non-metastatic castration-resistant prostate cancer <i>Rising PSA but no detectable tumors on imaging in patients who had previous hormone therapy</i>	<ul style="list-style-type: none"> ▶ Observation + continued hormone therapy for select patients ▶ Hormone therapy + androgen directed therapy*
Metastatic castration-resistant prostate cancer <i>Tumors detectable on imaging despite hormone therapy</i>	<ul style="list-style-type: none"> ▶ Androgen directed therapy* ▶ Radium-223 (for treatment of symptomatic bone metastases) ▶ Docetaxel or cabazitaxel chemotherapy ▶ ¹⁷⁷Lutetium-PSMA (if positive PSMA PET scan) ▶ Sipuleucel-T (if minimal symptoms) ▶ Olaparib or rucaparib (if DNA damage repair gene mutations are present, primarily BRCA1 and BRCA2)
Patient has exhausted all therapeutic options	<ul style="list-style-type: none"> ▶ Platinum chemotherapy ▶ Pembrolizumab (if MMR-deficient, MSI-high, or TMB-high)
Bone protection	<ul style="list-style-type: none"> ▶ Denosumab ▶ Zoledronic acid

*Discuss the options in this medication class with your doctor.

Note: At every stage, you can talk to your doctor about whether there is an active clinical trial that might be right for you.

External Beam Radiation Therapy (EBRT)

Radiation therapy can be used in multiple ways in men with metastatic prostate cancer. Use of radiation therapy in patients with mHSPC is discussed on page 70. In mCRPC, it is largely used as palliative care, that is, to alleviate symptoms due to the cancer.

One 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%–80% of patients will experience some degree of pain relief

after palliative radiation therapy. Typically, 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 instance where a doctor might recommend radiation therapy is when progressive disease within the prostate is 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.

Other situations where radiation therapy may be used include relieving pain from spinal cord compression, or proactively radiating an area of the bone that appears fragile to reduce the risk of fracture.

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

Bones are the most common site of prostate cancer metastasis, occurring in 85%–90% of patients with metastatic prostate cancer. Bone metastases interfere with the bone's normal health and strength. If they grow large enough, bone metastases 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, 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.

SIDE EFFECTS OF 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 treatments for localized disease, such as surgery and radiation therapy, please refer to [Possible Side Effects](#) on page 50. Remember that early management of side effects has been shown to help patients live longer, better lives. Communicate with your oncology team 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, androgen deprivation therapy (ADT), lowers testosterone and causes side effects related to low 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 be replaced by fat, especially around the abdomen.

Current research indicates a weak link between prolonged ADT and increased risk of dementia; in a subsequent study, no increased risk was shown between ADT and Alzheimer’s. While substitute therapies for ADT are an active area of research for the Prostate Cancer Foundation, ADT is currently a part of the standard of care. It’s important to be aware of the possible side effects, but it should not affect your decision to receive life-extending care.

Unfortunately, at this time, it is not possible to predict how severely you will be affected by lowering testosterone with hormone therapy. Research is underway to predict in advance which patients might experience which side effects. In the meantime, because hormone therapy 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.

Certain lifestyle changes, such as [diet and exercise](#), have been shown to relieve some 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.



Reducing red meat and increasing daily consumption of cruciferous vegetables (such as broccoli, cauliflower, and Brussels sprouts) can help during ADT and beyond.

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 health care team 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 your physician, nurse, or nutritionist to ensure that you are planning lifestyle modifications that are safe for you. There are other alternative strategies that can decrease 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 for 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 Androgen Directed Therapies

The newer androgen directed therapies (abiraterone, apalutamide, enzalutamide, and darolutamide) are used when prostate cancer has become resistant to traditional ADT and, increasingly, earlier in the management of advanced disease. They each have their own side effect profile.

- ▶ **Enzalutamide:** Side effects are mild but include fatigue, diarrhea, hot flushes, headache, frailty, falls, memory cloudiness and, very rarely, seizures.
- ▶ **Apalutamide:** The most common side effects are mild and include fatigue, hypertension, rash, hypothyroidism, diarrhea, nausea, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema (swelling of extremities).
- ▶ **Darolutamide:** Side effects are mild and include fatigue and weakness, and, rarely, laboratory abnormalities such as decreased numbers of neutrophils (a type of white blood cell) and liver function tests. Because darolutamide does not appear to cross the blood-brain barrier and get into the brain, it may be the better choice for patients at risk of seizures. It may also cause less fatigue and memory problems, though it has not been tested head-to-head to compare these side effects directly with enzalutamide and apalutamide.
- ▶ **Abiraterone (+ prednisone):** Side effects may include fatigue, high blood pressure, and electrolyte or liver abnormalities, and patients need to be monitored regularly.

Many of the side effects of ADT can be minimized with lifestyle changes that will also improve your overall health.

You and your doctor will need to consider your disease status and other medical conditions when choosing among these agents. For example, men with a cardiovascular disease history should be monitored closely when using these therapies, and consider management of any risk factors or disease with a cardiologist. Because abiraterone is given with prednisone, patients and their health care team must be aware of possible side effects associated with steroid treatment as well.

Side Effects of Chemotherapy

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 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, such as pegfilgrastim (Neulasta[®]); note that the use of this supportive medication is at the discretion of the physician, who must weigh the benefits of pegfilgrastim against its side effects. Despite use of pegfilgrastim, 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 make a plan for how to best handle further cycles of docetaxel.

Other common side effects of docetaxel are hair loss, diarrhea, nail changes, appetite loss, shortness of breath, and fluid retention. Less common side effects include low platelets which can result in bleeding, anemia, and reduced heart function. Most of these are mild, reversible, and treatable, and should not be a reason to avoid chemotherapy if you need it.

Side effects of cabazitaxel include reduced blood counts, and thus it is almost always given with pegfilgrastim to boost infection-fighting white blood cells. 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 of cabazitaxel include: fatigue, neuropathy, shortness of breath, headache, hair loss, abdominal pain, diarrhea, and low blood pressure. Based on trial results, the FDA now recommends a lower dose than was initially approved to improve tolerability for most patients; the dose can be increased in certain patients.

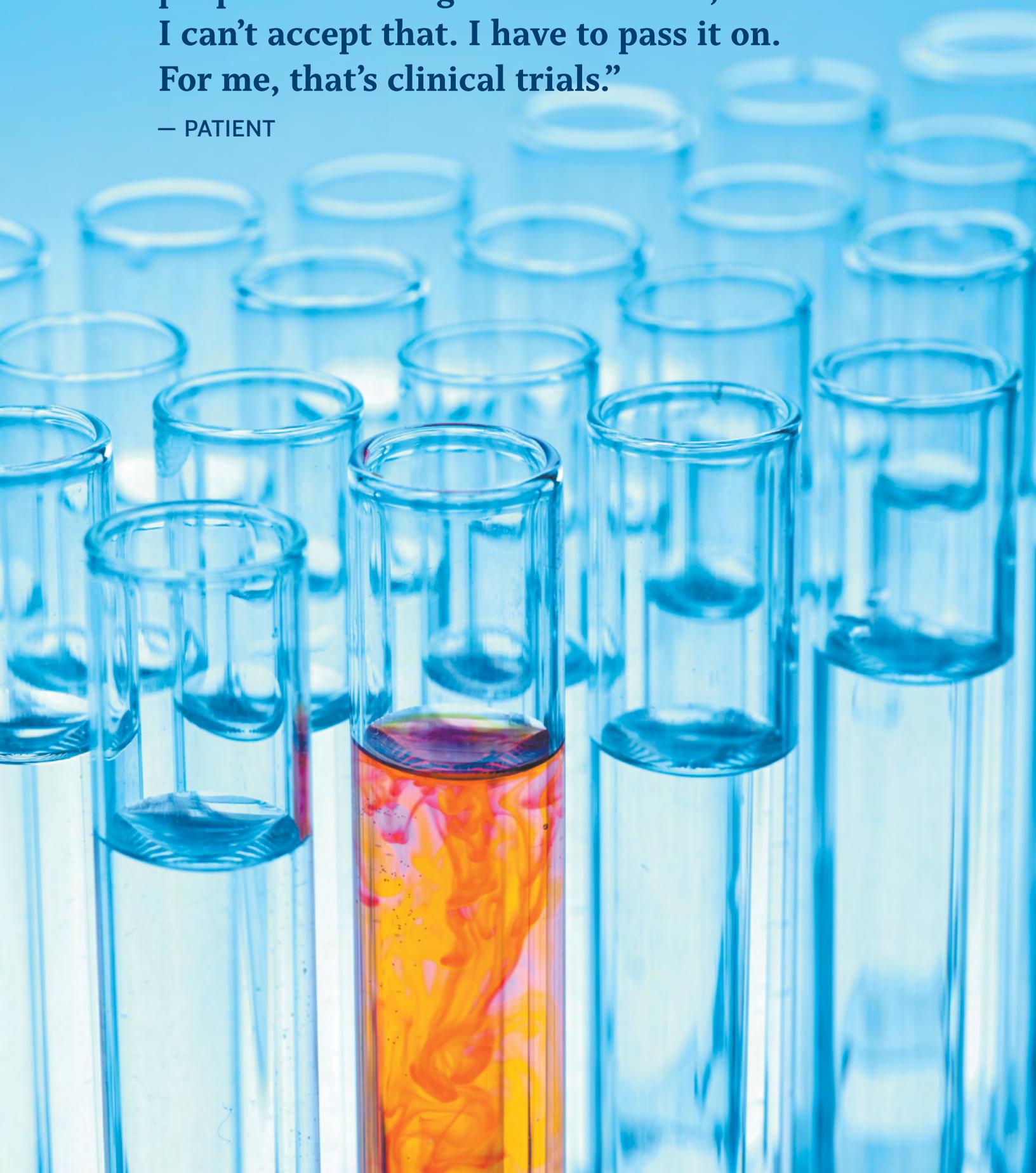
Regardless of the type of chemotherapy you are receiving, you will be monitored very closely by doctors, nurses, and pharmacists to make sure that all side effects are being addressed. Many of these side effects, especially fever and inability to keep food/drink down, need to be addressed right away—don't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



Tell your healthcare team if you experience side effects of treatment. Early management of side effects can improve your quality of life.

“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 unique biology 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 individual 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. Once that level of identification is possible, custom treatments have the potential to be more effective with less guess work. Since cancer is a “[genomic disease](#), that is, most cancers involve mutations of various genes, precision oncology is one of the most exciting fields in research today.

Because every cancer fingerprint can be 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 trial and error—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. Tests that use either

CANCER TESTING TERMINOLOGY

The terms used for the many different types of testing can be confusing. **Biomarker testing** looks for characteristics in cancerous tumor tissue that may be used in medication selection. These characteristics may have been present when the tumor started, or may be acquired as the tumor grows. **Genetic testing for inherited mutations** is assessed through a blood or saliva sample. It refers to mutations (changes) in your genes (DNA) that you inherited from your parents. Results of genetic testing may be used to guide treatment and/or to inform family risk of cancer.

DID YOU KNOW?

25%–30% 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. New drug development for patients with DNA repair mutations is an active area of research for the Prostate Cancer Foundation, resulting in the recent approval of 2 medicines called PARP inhibitors (see page 75).

tumor biopsies or your blood to analyze the genomic and molecular make-up of your cancer can help.

Here's one example of just how precise the right treatment can be. Scientists are working to determine whether your prostate cancer is fueled by hormones produced outside of the testes, therefore decreasing the effectiveness of hormone therapy alone for you. About half of all men have a genetic variation called HSD3B1(1245C) that allows prostate cancer to make its own dihydrotestosterone. If you have low-volume advanced prostate cancer that is being treated with ADT, your tumor may be more likely to become resistant if you have the more active HSD3B1(1245C) gene, because the cancer can make its own “fuel.” In the future, doctors may routinely use test results for this gene variation to guide treatment.

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. Unfortunately, some treatments may be so new that even your doctor isn't up to date on their availability. For the very latest information on emerging precision therapies, please visit pcf.org.

EMERGING NEAR-TERM THERAPIES

There are over 800 ongoing clinical trials in prostate cancer just in the U.S. 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, new treatments, or improved ways to use therapies that have already been FDA-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

Since the last printing of this guide, PARP inhibitors have been FDA-approved for patients with metastatic castration-resistant prostate cancer (mCRPC) whose cancer has progressed despite other treatments and who have mutations in certain genes. See Chapter 5, *Therapies for Advanced and Metastatic Prostate Cancer*.

PSMA Radionuclide Therapy

This is the newest class of treatment for advanced prostate cancer. In March 2022, ¹⁷⁷Lutetium-PSMA-617 was FDA-approved for patients with mCRPC whose cancer has progressed despite treatment with an androgen directed therapy and taxane-based chemotherapy. See Chapter 5.

THE FUTURE LANDSCAPE OF PROSTATE CANCER PRECISION THERAPY

A few of the most exciting emerging therapies, which are currently being tested in clinical trials, are discussed below.

Precision Testing

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, PIK3CA/PIK3CB, AKT1/2/3, RAF, Wnt, CDK12, 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 biomarker testing of their tumor and genetic testing for an inherited mutation to determine whether they may carry any actionable inherited or acquired mutations.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a class of immunotherapy that activate tumor-killing immune cells. Checkpoint immunotherapy alone (not in combination with other treatments) may only work for a subset of prostate cancer patients, and studies are underway to determine how best to identify these men. In 2017, the FDA approved the checkpoint inhibitor pembrolizumab (Keytruda®) for patients with solid tumors that have mutations in mismatch repair genes (MMR), exhibit microsatellite instability (MSI), and/or have a high tumor mutational burden (TMB-H). Recent studies suggest that patients with advanced prostate cancer whose tumors have lost both copies of the CDK12 gene may respond to checkpoint immunotherapy.

Many studies are underway in prostate cancer to test checkpoint inhibitors, including pembrolizumab and ipilimumab (Yervoy®), in combination with various therapies including PARP inhibitors, cancer vaccines, and radiation therapy.

CASE STUDY: HOW GENES AND TREATMENTS ARE BEGINNING TO WORK ACROSS CANCER TYPES

In prostate cancer, we currently have experimental treatments in the works for dozens of genes, but only a few are FDA-approved. One treatment that is FDA-approved based on a mutation found in tumors is pembrolizumab (Keytruda®) for tumors with microsatellite instability (MSI), mutations in a mismatch repair (MMR) gene, or high tumor mutational burden (TMB-H). MMR genes are proteins that "proofread" and edit DNA in order to prevent mistakes that can lead to mutations and cancer. Defects in MMR gene function can be detected through testing. While only about 3%–4% of advanced prostate cancer patients have MSI, approximately 15% of colon cancer patients do. Because testing for MSI was first developed and optimized for colon cancer, not all MSI tests may detect all prostate cancer with MSI; talk to your doctor about more precise testing.



Everything about you—from your cancer to your immune system to the bacteria that inhabit your body—is unique. More and more, scientists are thinking of cancer treatment as a personalized plan.

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. There are multiple ongoing early-phase clinical trials of CAR T cells targeting prostate cancer.

PROSTVAC

There are many strategies to activate the immune system to target and kill prostate cancer. One strategy is the use of **cancer vaccines**, which instruct immune cells to identify and kill cells that express certain prostate cancer-associated proteins. PROSTVAC is a vaccine that activates the immune system to target prostate specific antigen (PSA), a protein specifically expressed by prostate cancer cells (same PSA as in the PSA test). PROSTVAC has not shown efficacy as a single agent in clinical trials, but is currently being tested in combination with other therapies.

Microbiome

The microbiome is the collection of microorganisms living in your body and, in particular, your gut. So, what's that got to do with cancer? New research is revealing that it could be a lot. Studies suggest that the gut microbiota can affect the immune system and may influence how well patients respond to certain cancer treatments. Doctors now think that for your body to stay healthy and cancer-fighting, it's important to have the right diversity of bacteria in your gut, but there's still a lot to learn about how this translates to improved patient outcomes. Some types of microbes in your urinary tract also may be linked to prostate inflammation and risk of prostate cancer. Exploring the relationship between your microbiome and cancer is an active area of research for the [Prostate Cancer Foundation](#).

A LIFETIME “POLYGENIC” RISK SCORE FOR PROSTATE CANCER

There are 100s of genes related to prostate cancer that you inherited from your parents. We now know there are several *combinations*—think of it like a certain hand of cards you are dealt when you are born—that can increase your risk of prostate cancer. Thanks to the generosity of Robert F. Smith, PCF is funding research on a test that looks across these genes, someday allowing doctors to predict how likely it is that any man may get prostate cancer in his lifetime. This “polygenic” risk test will be especially important for Black men, who are at higher risk of aggressive disease. It will provide critical information for true “precision screening:” hyper-vigilance for certain men at high risk, and less invasive for those at lower risk.

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?

Right now, there are nearly 100 phase 3 trials and more than 500 phase 1 and 2 trials related to prostate cancer treatment in progress in the United States alone. These trials focus on the full breadth of the prostate cancer experience, looking at everything from better treatments for localized prostate cancer, to life-prolonging drugs for advanced disease, to lifestyle and prevention changes which can improve the lives of patients and their families. Treatments that are approved will further improve outcomes for patients and join the multiple life-extending and life-improving therapies that are already in use.

CLINICAL TRIALS: HOW TO GET INVOLVED

Finding new treatments, and how to best use new treatments, is the work of clinical trials. Over and over again, there are stories of men with what was thought to be incurable prostate cancer who were all but cured on a clinical trial.

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 potentially 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.

Drugs for Advanced Prostate Cancer

There are currently more than 20 drugs FDA-approved for the treatment of advanced prostate cancer. As an example of the importance of clinical trials, remember that nearly all of them had to go through phase 1, 2, and 3 clinical trials in order to receive FDA-approved designation. Of these drugs, 13 were developed with direct early-stage support from the Prostate Cancer Foundation.

In 1996, in response to a critical unmet need for clinical trials in prostate cancer research, PCF created the Therapy Consortium. In 2005, PCF partnered with the Department of Defense to transform this organization into the Prostate Cancer Clinical Trials Consortium. Since 2006, consortium members have enrolled more than 8600 men with prostate cancer in over 230 trials.

Treatment for Prostate Cancer	Year of FDA Approval
Estramustine	1981
Leuproreotide acetate	1985
Flutamide	1989
Bicalutamide	1995
Mitoxantrone + prednisone	1996
Nilutamide	1996
Goserelin acetate	1998
Triptorelin	2001
*Zoledronic acid	2002
*Docetaxel	2004
Histrelin acetate	2004
Degarelix	2008
Cabazitaxel	2010
*Sipuleucel-T	2010
*Denosumab	2010
*Abiraterone	2011
*Enzalutamide	2012
*Radium-223	2013
*Pembrolizumab	2017
*Apalutamide	2018
*Darolutamide	2019
*Rucaparib	2020
*Olaparib	2020
Relugolix	2020
* ¹⁷⁷ Lutetium-PSMA	2022

*Supported by PCF-funded research

GET INVOLVED!

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

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 often still receive the minimum standard of care.**

Clinical Trials

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

Phase 1: Test a new agent on a small number of 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, 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 mutations in BRCA1 and BRCA2 genes that increase risk for not only breast and ovarian cancers, but also for prostate, pancreatic, gastrointestinal cancers, and others.

Prostate cancer has long been recognized to have a familial component. In fact, of all human cancers, prostate cancer is the most common among family members, with 57% of prostate cancer attributable to genes that run in families. If you 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.

Revisiting Family Risk

If a family history of prostate cancer or genetic predisposition exists, it is all the more important that your family understands the full picture of risk related to prostate cancer. There are 4 major factors that influence risk for developing prostate cancer. Because detection (and successful treatment, if needed) of prostate cancer 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. The average age at diagnosis of prostate cancer in the United States is 69 years, however, prostate cancer can occur in much younger men.

Race: Black men are about 75% more likely to develop prostate cancer and have more than twice the risk of dying from it. The reasons are complex—from genetics, to social determinants of health, to systemic racism—which can lead to worse outcomes in other diseases as well.

Family history and inherited (aka “germline”) genetic mutations: A man with a father or brother who had prostate cancer may have a twofold-increased risk for developing it himself. This risk is further increased if the cancer was diagnosed at a younger age (less than 60 years of age) and/or affected 3 or more family members. It is important to discuss family history of prostate cancer with your family and your healthcare team. Because many cancers share similar genes, it's important to also know and discuss your family history of all cancer, but especially breast, ovarian, colon, or pancreatic. See [Prostate Cancer Genes in Families](#) on page 91. PCF-funded research has shown that men of West African descent may have an increased risk for aggressive disease, based on inheritance of certain gene combinations for prostate cancer.

Consider: Prostate cancer is over 8 times more common in Western cultures than in Asia; moreover, when Asian men migrate to Western countries, their risk of prostate cancer increases over time. Why? Genetics, environment and lifestyle factors, and screening protocols may all play a role. Researchers are now looking at prevention strategies which may shed light on this mystery.

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 both male and female members of their extended family.

Should My Family Members 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. Since prostate cancer can skip a generation but “run in families,” both screening and genetic testing should be considered for the entire family.

While there is ongoing debate about the risks and benefits of prostate cancer screening, proponents argue that early detection offers a better chance of cure, especially for aggressive types of prostate cancer. On the other side of the argument is a concern with overtreatment. Because most prostate cancer is slow-growing, some people argue that the risks of side effects from treatment outweigh the benefits of treatment.

In reality, both sides of this argument are true. For men at high risk because of race or family history, early screening can be life-saving. For men with slow-growing low-risk disease, **active surveillance** (i.e., delaying treatment through the use of frequent monitoring, see page 35) is an excellent option that avoids side effects. In both cases, what PCF refers to as “precision screening” is the key to success. **Overtreatment, not screening, should have the bad rap; don’t shoot the messenger.**

The U.S. Preventive Services Task Force (USPSTF) is an independent panel of experts that issues recommendations on disease screening. In 2018, the USPSTF recommended shared decision-making for PSA screening. As the potential benefits and harms of PSA-based screening are about equal in men age 55 to 69 years, the decision to screen should be an individual one. For men age 70 years and older, USPSTF recommends against screening for prostate cancer, with the rationale that potential benefits do not outweigh the harms. For more info on the latest USPSTF recommendations visit pcf.org/uspstf-faqs.

Other professional organizations, such as the American Society of Clinical Oncology, National Comprehensive Cancer Network, 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.

In men expected to live less than 10 years, PSA screening should be considered carefully, since the rigor of some treatments and side effects can actually lessen life expectancy as well as quality of life.

BEGIN TO TALK TO YOUR DOCTOR ABOUT SCREENING AT AGE

- 40 ► If you have a family history of prostate or other cancers in a first-degree relative, are Black, or have known BRCA 1/2 mutations
- 45 ► If you have no family history of prostate cancer and you are not Black

When to Start—and Stop—Screening

Regardless of your age, the Prostate Cancer Foundation recommends that you practice “precision screening,” and consult with your doctor to come up with a personal screening plan that’s right for you. Go to pcf.org/screen and use the screening tool as a guide to start a conversation with your doctor.

For men with a family history of prostate, breast, ovarian, pancreatic, or colon cancer in a first-degree relative, begin a conversation with your doctor at age 40. Because Black men are more likely to have aggressive disease, it is recommended that they begin the conversation at age 40 as well. Lastly, because we now know that genes that run in families can affect prostate cancer risk, if you have a personal or family history of BRCA1 or BRCA2 mutation (most infamously responsible for hereditary breast cancer), begin discussions about screening at age 40, or, better yet, consider a clinical trial for early detection of prostate cancer. For average-risk men, the National Comprehensive Cancer Network (NCCN) recommends starting this discussion at age 45.

Shared decision-making (or a discussion of the pros and cons of screening) is an important part of the process. Research is ongoing to further illuminate the benefits and harms associated with screening in men above the age of 70.

If you are a healthy man over 70, be sure to discuss continued screening with your doctor.

Screening and Biopsy Decisions

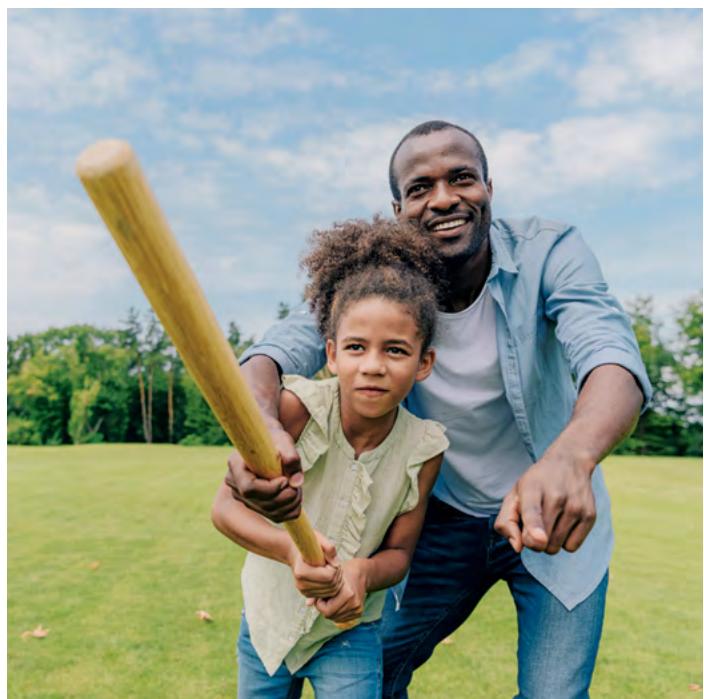
PSA screening may reveal results that prompt a doctor to recommend a biopsy. However, the result may create more confusion if the PSA is mildly elevated. Fortunately, there are many other supplementary tests and considerations that can help a man who is undergoing screening decide whether a biopsy is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

- ▶ Digital rectal exam results
- ▶ Free PSA test (measures PSA not bound to proteins in blood; <10% Free PSA indicates greater risk of having cancer, <25% is concerning)
- ▶ PSA velocity or the rate of rise over time (faster increases mean more risk)
- ▶ PSA density, or the PSA per volume of prostate (higher density means more risk)
- ▶ PSA-based markers (e.g., Prostate Health Index, 4K score)
- ▶ EPI test score >15.6
- ▶ Other markers, a urinary PCA3 or SelectMDx 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 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.

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 that, 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 more than 10% have inherited mutations in cancer risk genes such as BRCA1, BRCA2 and at least 18 other newly-discovered genes that may be important to risk of prostate cancer and other types of cancer.



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

Over 20 different genes have been identified that run in families with prostate cancer (hereditary prostate cancer).

Because many of the genes and cancer pathways that drive prostate cancer occur across other cancers, PCF's work now has overlap in at least 70 other cancers (see chart on page 94). This is important because it highlights that men should be aware of their family history of all cancer—i.e., not just prostate cancer, but also breast, ovarian, pancreatic, leukemia, and other cancers. Having a sister with breast cancer diagnosed at an early age (for example, in her 40s or younger) may be valuable information for a man to know and share with his doctor. Conversely, your prostate cancer may imply a high cancer risk for both your male and female family members.

There can also be other mutations that occur after birth which drive cancer development and progression. Scientists have identified over 97 of these “somatic mutations” implicated in prostate cancer.

Do You Carry A Genetic Mutation?

Talk to your doctor about a referral to a genetic counselor if you have prostate cancer and any of the following risk factors. Ask family members for more information if needed.

YOU

- ▶ Diagnosis of high-risk, regional, or metastatic prostate cancer
 - Biopsy shows intraductal carcinoma or cribriform pattern
- ▶ Diagnosis of one or more of the following cancers: breast, gastrointestinal, colorectal, pancreatic, brain, urinary tract, biliary tract, or melanoma
- ▶ Ashkenazi Jewish ancestry

YOUR FAMILY

- ▶ One or more close blood relatives with prostate cancer diagnosed at age 60 or younger, or with high-risk, regional, or metastatic prostate cancer at any age
- ▶ 2 or more close blood relatives with prostate or breast cancer
- ▶ One or more close blood relatives with breast, colorectal, or endometrial cancer diagnosed at age 50 or younger, or with male breast cancer, ovarian cancer, or pancreatic cancer
- ▶ Blood relative with a known cancer risk gene mutation (e.g., BRCA1, BRCA2, Lynch syndrome)
- ▶ 3 or more members on the same side of the family with one or more of the following cancers: colorectal, urinary tract, brain, gastric, or multiple other cancers

WHAT DO WE KNOW ABOUT GENE MUTATIONS AND PROSTATE CANCER?

Researchers are beginning to categorize gene mutations for prostate cancer by whether they 1) increase your risk of getting the disease or 2) increase the aggressiveness of advanced disease. This may someday yield a “polygenic risk score” for every man to indicate his lifetime risk of getting prostate cancer, based on his full gene profile.

Family members who learn that they are carriers need to discuss their findings with genetic counselors and their doctors to better understand their cancer risks, options for early detection, and how to reduce risk for various other forms of cancer.

There is still much that scientists are learning about how these gene mutations relate to personal risk, disease progression, treatment, and family risk. Some tests may return results called “variants of unknown significance.” That is why it is critical to consult a genetic counselor. Patients and families with these types of mutations may consider participating in research registries to help doctors and researchers learn more about those specific variants.

For some genes that are better studied, there may be clear screening recommendations and risk-reduction strategies. However, even 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. It is strongly recommended that families consider consulting doctors at a top-tier or academic medical center. Usually, these centers are actively engaged in the latest research and treatments and can offer the most updated information, recommendations, and plan if you are found to have a cancer risk mutation.

“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 an inherited mutation in BRCA1, BRCA2, or other genes that increase risk for prostate cancer, this has critical implications for all his family members. If male or female family members have inherited the same mutation, they may be at increased risk for several types of cancer, depending on the gene.

Men who find they are gene mutation carriers should talk with a genetic counselor to 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 increased risk for certain cancers.

THE NUANCES OF GENETIC TESTING

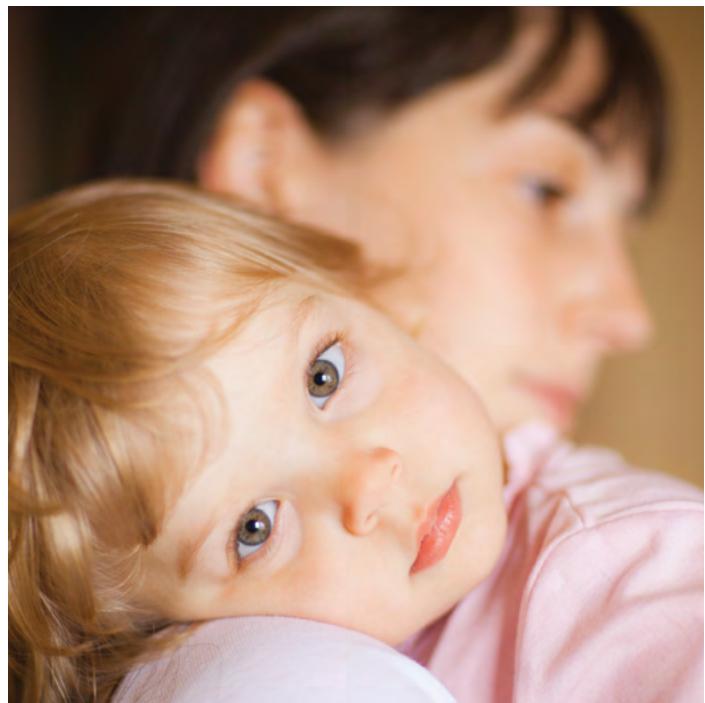
Many genetic testing companies are offering services to find hereditary mutations in cancer-associated genes. It is critical to be aware that not all gene mutations have been extensively studied, and **the risk for any given cancer associated with any given mutation is not always clear.** There are several well-studied mutations that researchers believe are more often present in patients with cancer, and other mutations with some association with cancer risk that is not yet well understood. Finally, there are many “variants of unknown significance,” where we do not yet know whether the change in the gene increases cancer risk or is benign.

WHAT'S THE DIFFERENCE BETWEEN GENETIC TESTING AND BIOMARKER TESTING?

Genetic testing for inherited mutations (also known as germline genetic testing or sequencing) often uses a blood test or saliva test to look at your DNA only for inherited gene mutations—those that you inherited from your mother or father that may increase your risk for developing cancer.

Biomarker testing (also known as somatic or tumor sequencing) is performed on tumor tissue samples obtained from biopsies or surgery. The testing may look at DNA, RNA, or proteins. Your tumor may contain mutations that are inherited or have been acquired during disease progression. This test is usually performed for the purpose of treatment decision-making. (Note that biomarker testing may refer to testing for other characteristics, in addition to gene mutations.)

Both kinds of testing have the potential to suggest presence of inherited mutations that may be important to you and your family.



The same cancer gene errors that PCF is researching for prostate cancer apply to 7 of the top 10 pediatric cancers (so far).

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. There are also telehealth genetic counseling services available.

If your genetic testing returns a result with a “pathogenic variant”—that is, you have an inherited gene mutation linked to prostate cancer risk or growth—it is important to consult with your medical team and seek genetic counseling. Remember, new clinical trials and studies are emerging regularly to find new treatments that might be relevant for you. Go to pcf.org/news for more information on the latest research and drug approvals.

COMMERCIALLY AVAILABLE GENETIC TESTING SERVICES

Whenever possible, seek the advice of a genetic counselor and/or your doctor to help you understand which tests are most appropriate for you, what they mean, and how they affect your care—ideally before you take such a test. There are also telehealth genetic counseling services increasingly available. After gathering information and understanding benefits, risks and limitations of testing, you may ultimately choose to proceed with commercially available testing. Several companies offer genetic testing for inherited cancer risk, and have the benefit of accessibility. Out-of-pocket costs vary (often in the range of \$250–\$350, depending on the number of genes in the panel). Consumers use a kit to submit a saliva sample. However, more genes is not always better, and can sometimes lead to more questions than answers, so talk to your doctor before choosing a test. Whether the test is covered by insurance depends on your insurance benefits. Consumers receive a report with their results and are encouraged to discuss with their medical team, if they have not done so already. Access to a genetic counselor by telephone before or after the test may be included in the fee. Three such companies are:

Color: Offers panels (in 3 different sizes) of genes involved in hereditary cancers, including at least 11 genes implicated in prostate cancer.

Invitae: Offers a Cancer Screen panel of at least 61 genes to assess the risk of hereditary cancer, including prostate cancer.

Ambry: Offers panels for several specific cancers, including prostate cancer, as well as larger, more comprehensive panels.

Of note, recreational tests (such as 23andme) should not be considered an adequate substitute for comprehensive genetic testing for inherited cancer risk mutations.

PCF'S IMPACT ACROSS ALL CANCERS

Particularly for men with advanced or aggressive disease—that is, whose disease is most resistant to standard treatment—biomarker- or gene mutation-directed therapies may be especially effective. PCF believes that gene targets and pathways may be the bridge to unlocking treatments for all cancer, not just prostate cancer. PCF genetic research in prostate cancer has been able to add to the research and development on tumor mutations in more than 70 other forms of cancer.

- | | | | | |
|-------------|---------------|-----------|------------|---------------------------|
| ► Brain | ► Thymus | ► Kidney | ► Blood | ► Ovary |
| ► Eye | ► Lung | ► Colon | ► Sarcoma | ► Uterus |
| ► Lip | ► Liver | ► Bladder | ► Prostate | ► Childhood brain cancer |
| ► Neck | ► Stomach | ► Rectum | ► Testicle | ► Childhood blood cancer |
| ► Thyroid | ► Gallbladder | ► Skin | ► Breast | ► Childhood kidney cancer |
| ► Esophagus | ► Pancreas | ► Nerve | ► Cervix | |

THE FUTURE LANDSCAPE OF CANCER

For years, doctors focused on cancer as an organ-site disease, e.g., you had breast cancer, or colon cancer, or prostate cancer. Thanks to some significant discoveries funded by PCF, we now know cancer is too complex to be studied in a single site in the body. Cutting-edge research is now targeting the mechanisms cancer uses to grow, which may be shared across many cancer types. In treating prostate cancer, this work will likely impact hundreds of forms of disease, including most major forms of cancer in children.

For more information visit impact.pcf.org.

PREVENTION

The ultimate goal is to prevent men from ever developing prostate cancer. Researchers are finding new strategies to help men reduce their odds of getting prostate cancer and, if diagnosed, to improve their survival and quality of life during treatment. Note that screening does not lead to prevention, but only to earlier detection.

DIET AND EXERCISE

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.

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.

Beyond genetics, diet and exercise are key to reducing prostate cancer risk or recurrence. There is much hope on the horizon for men with prostate cancer and their families. Continuing to be prudent with regard to risk factors, screening recommendations, and diet and



Fish, berries, cooked tomatoes, and broccoli may act as anti-inflammatory foods to help protect your prostate health.

exercise changes can help men with prostate cancer live longer and better lives. For more information, download PCF's comprehensive prevention and wellness guide, *The Science of Living Well, Beyond Cancer*, at pcf.org/guides.

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 45 or over, or if you are age 40 or over and are Black or have a family history of prostate cancer, regular exercise and a good diet are even more critical for reducing risk; consider regular PSA tests, and, if indicated, rectal examinations, 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.

► CHECKLIST: LIFESTYLE CHANGES FOR PROSTATE CANCER PREVENTION

- Adopt an “anti-inflammatory diet,” low in red meat, sugar, processed foods, and dairy products, and high in foods that fight inflammation, like some of those listed below.
- Eat fewer calories AND exercise more to maintain a healthy weight. Vigorous exercise, within the bounds of safety for your personal physical fitness level, has been shown to reduce a man’s chance of developing lethal forms of prostate cancer.
- Watch your calcium intake. Very high amounts of calcium may increase risk of aggressive prostate cancer. Try to get most of your calcium from plant-based food sources (e.g., almonds, tofu, leafy greens) rather than supplements, unless your doctor has advised otherwise.
- Swap red meat for plant-based protein and fish. Saturated fat in red meat is a cause of inflammation, which is associated with cancer and other chronic diseases. Avoid trans fatty acids (e.g., margarine, packaged baked goods).
- Try to incorporate cooked tomatoes, whose high lycopene content may help to protect against the cellular damage associated with cancer.
- Cook with extra virgin olive oil. Consider 1-3 tablespoons per day, depending on your size. Make sure you use the first pressed “extra virgin” oil.
- Incorporate cruciferous vegetables (like broccoli and cauliflower) into many of your weekly meals. One study found that eating broccoli can help shift your intestinal flora away from the types of bacteria that are related to prostate cancer.
- Soy has been a topic of health debate, but some research suggests that eating soy is associated with a lower risk of prostate cancer, and it can be part of a general heart-healthy diet.
- Green tea’s high antioxidant properties may be beneficial in warding off cancer.
- Avoid smoking for many reasons. In particular, a recent study revealed that men who smoked during prostate cancer treatment had a higher likelihood of metastasis.
- Limit alcohol to one drink per day. If you do drink, consider a glass of red wine. Red wine contains resveratrol, which has been shown to possibly have cancer-fighting properties.
- Enjoy coffee, if you drink it. Studies suggest that drinking coffee, 1-2 cups per day, can help prevent aggressive forms of prostate cancer. Decaf is fine, too: The benefits seem to come from compounds in coffee other than caffeine.
- Seek medical treatment for stress-related conditions, high blood pressure, diabetes, high cholesterol, and depression. Treating these conditions may save your life and will improve your survivorship with prostate cancer.
- Avoid over-the-counter supplements, unless recommended by your doctor or nutritionist. While a multivitamin is not likely to be harmful, you probably don’t need it if you follow a healthy diet with lots of vegetables, whole grains, fish, and healthy oils. Ask your doctor about herbal supplements, as some may harm you or interfere with treatment.
- Relax and enjoy life. Studies have shown that the stress hormone cortisol can interfere with cancer cell death. Reducing stress in the workplace and home will improve your survivorship and lead to a longer, happier life.

Basic Sofrito Recipe

Sofrito is a tomato-based sauce that is used as a base in cooking in many cultures. The lycopene in cooked tomatoes may act as a protective antioxidant. Add that to the latest research on olive oil and you’ve got a great cancer-fighting food.

This base recipe can be multiplied or modified with different herbs and spices, to transport it across the globe.

- 1 pound of tomatoes
- 1 medium onion
- 1 red pepper
- 3 cloves of garlic
- 1/3 cup of extra-virgin olive oil
- Fresh herbs to taste
- Salt, to taste

Finely chop all ingredients. Heat oil and add everything at once to the pan. Cook 20-30 minutes. Let cool, and refrigerate or freeze.





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