

PROSTATE CANCER FOUNDATION

PATIENT GUIDE TO RECURRENT AND METASTATIC PROSTATE CANCER

A comprehensive resource on diagnosis, treatment, and side effects for patients with recurrent and metastatic prostate cancer and their families.



“I’m happy that we’ve got it to a point where they can manage it now. Don’t let it attack you. You attack it.”

– PATIENT

About this guide

There are no two ways about it: being diagnosed with cancer is hard and 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 thousands and thousands of cancer-related webpages, blogs, and videos available at your fingertips. But it is important to acknowledge that this is not always helpful. A cancer diagnosis—or a recurrence—can be disorienting, and the overwhelming volume of information available can be more of a burden than an aid.

This guide consolidates the most current, accurate information about advanced prostate cancer into one focused resource. It is intended for any man who has been newly diagnosed with metastatic prostate cancer, or who is currently receiving treatment, and continues to seek support for side effects or guidance on health practices. This guide is also intended for patients who have previously been treated for localized prostate cancer and are now seeing their PSA rise. For patients with more advanced prostate cancer states that have become resistant to standard treatment, this guide covers cutting-edge precision therapies, among many other options. This guide is also intended for any loved one or caregiver who wants to get essential information to help patients navigate their prostate cancer journey. Lastly, as we are beginning to recognize the genetic underpinnings of cancer, this guide is also for any family member who seeks to understand how shared genes affect their own short- and long-term risks.

WHICH PCF PROSTATE CANCER PATIENT GUIDE IS FOR ME?

PCF produces two patient guides: one for Localized Prostate Cancer and another for Recurrent and Metastatic Prostate Cancer.

If you have just been diagnosed with prostate cancer that has spread (metastatic), you have treatment options. If you have previously been treated for prostate cancer and your PSA is rising, or your doctor suspects that your cancer may have recurred, this guide is for you. If you have been diagnosed with prostate cancer and your doctor has told you that your cancer is early stage, still in the prostate, localized, or low grade, please consult our companion guide, the PCF *Patient Guide to Localized Prostate Cancer*.

We gratefully acknowledge the scholarly expertise and contributions of our medical editors: Heather Cheng, MD, PhD (University of Washington, Fred Hutchinson Cancer Center), Stacy Loeb, MD, MSc, PhD (hon) (New York University and Manhattan VA), Andrea Miyahira, PhD (Prostate Cancer Foundation), Alicia Morgans, MD, MPH (Dana-Farber Cancer Institute), Jones Nauseef, MD, PhD (Weill Cornell Medicine), Rashid Sayyid, MD, MSc (University of Toronto), Daniel Spratt, MD (University Hospitals Seidman Cancer Center and Case Western Reserve University), and lead reviewer Zachary Klaassen, MD, MSc (Wellstar MCG Health, Georgia Cancer Center).

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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 seminal fluid components. Prostate cancer occurs when a normal prostate cell becomes altered and starts growing in an uncontrolled way. Prostate cancer cells form masses of abnormal cells known as tumors.

How Common is Prostate Cancer?

Approximately one in eight men in the U.S. will be diagnosed with prostate cancer during their lifetime. Prostate cancer is the second most commonly diagnosed type of cancer in men, after skin cancer. In 2023, it is estimated that more than 288,000 new cases will be diagnosed in the U.S., and about 1.4 million men were diagnosed globally in 2020. The number of patients in the U.S. living with metastatic prostate cancer is estimated to be about 120,000 and is projected to be more than 190,000 by 2030.

Prostate Cancer Outcomes

More than 80% of all prostate cancers are detected when the cancer is in the prostate or the region around it. Many patients can be cured of their disease with surgery or radiation therapy alone, or may even be able to monitor their cancer closely without immediate treatment. However, prostate cancer comes in many forms, and some prostate cancers can be aggressive even when they first appear to be confined to the prostate. Between 30%–50% of patients initially treated for localized disease experience recurrence, even many years later.

New therapies and treatment strategies are increasingly available for patients with recurrent and advanced prostate cancer.

Over the last dozen years in the U.S., an increasing number of patients are receiving an initial diagnosis of metastatic prostate cancer—that is, cancer that has already spread outside the pelvis to bones or other organs. And while the death rate from prostate cancer had been declining consistently since its peak in 1993, it is now leveling off. These concerning trends have been linked to a national decrease in prostate cancer screening starting around 2008, based on recommendations by the United States Preventive Services Task Force, which have since been revised in 2016.

Yet, even for patients with the most aggressive forms of prostate cancer, there is growing optimism. New therapies, combination treatments, and clinical trials have become increasingly available in recent years.

Risk Factors

There are three well-established risk factors for increased prostate cancer diagnosis: older age, Black race, and family history. The older you are, the more likely you are to be diagnosed with prostate cancer. The average age of men diagnosed with prostate cancer is 66 years. Nearly 60% of all prostate cancers are diagnosed in men over the age of 65. However, it is important to note that a substantial number of cancers are diagnosed in younger men, who can develop aggressive cancers that require early, aggressive treatment.

One in six Black men will be diagnosed with prostate cancer in their lifetime (compared with one in eight white men), and they are more than twice as likely to die from the disease. Researchers are still working to understand the root cause of these disparities. They are thought to be related to a complex interplay of factors including environmental exposures, socioeconomic factors, limited access to timely screening and medical care, and genetics.

Over **20** genes

have been discovered that are linked to inherited prostate cancer.



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

There are more than **25** FDA-approved treatments for prostate cancer.

1 in 8 U.S. men will develop prostate cancer in his lifetime.



2 minutes

In 2023 in the U.S., a new case is diagnosed every 2 minutes.

10 THINGS TO KNOW

Black men are about **70%** more likely to develop prostate cancer.

70%

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

Transformational research is helping to reduce death and suffering from 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.

Genes that increase the risk of cancer can run in families. Genetic factors contribute to more than half (58%) of all prostate cancers, which makes prostate cancer one of the most “heritable” of all cancers. Men who have a close relative with prostate cancer, such as a biological father or brother, may be twice as likely to develop the disease, while those with 2 or more relatives may be up to 4 times as likely to be diagnosed. 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. Although known to be a very heritable cancer, not all of the specific genes contributing to the risk have yet been identified. [For more on family risk, see The Genetics of Cancer Risk, page 47.](#)

The three major risk factors for prostate cancer are older age, Black race, and family history of the disease.

Obesity and smoking are among other factors associated with increased risk of aggressive prostate cancer and worse disease outcomes. Men who are overweight or obese are at greater risk of ultimately developing an aggressive form of prostate cancer. This is further complicated by research that 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. Exposure to toxins such as Agent Orange may increase the risk of aggressive prostate cancer.

Symptoms

If you have recently been diagnosed with prostate cancer, you may be asking yourself if there were 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 the disease may be silent for many years. Most urinary symptoms that men experience are due to other causes. However, if the disease has significantly enlarged, causing a “mass effect,” or has spread outside the prostate, 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
- ▶ 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

Prostate cancer rarely causes symptoms; the disease may be silent for many years.

MEDICAL BASICS

The more you know about the normal development and function of the prostate, where it is located, and what it is attached to, the better you can understand how prostate cancer develops and impacts a man's life over time.

Anatomy of the Prostate

The **prostate** is a small gland about the size of a table tennis ball or a walnut. It sits under the bladder and in front of the rectum. The prostate is only present in people who are biological males. It is not essential for life, but it is important for reproduction, because it supplies fluids needed for sperm to survive. Sperm are not made in the prostate; they are made in the **testes** and travel to the prostate through the vas deferens.

The **seminal vesicles** are structures shaped like rabbit ears that store and secrete a large portion of the ejaculate. These structures sit behind 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 and help with maintenance of urinary control. They travel from the lower spine forward through the pelvis to the penis.

Because 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.

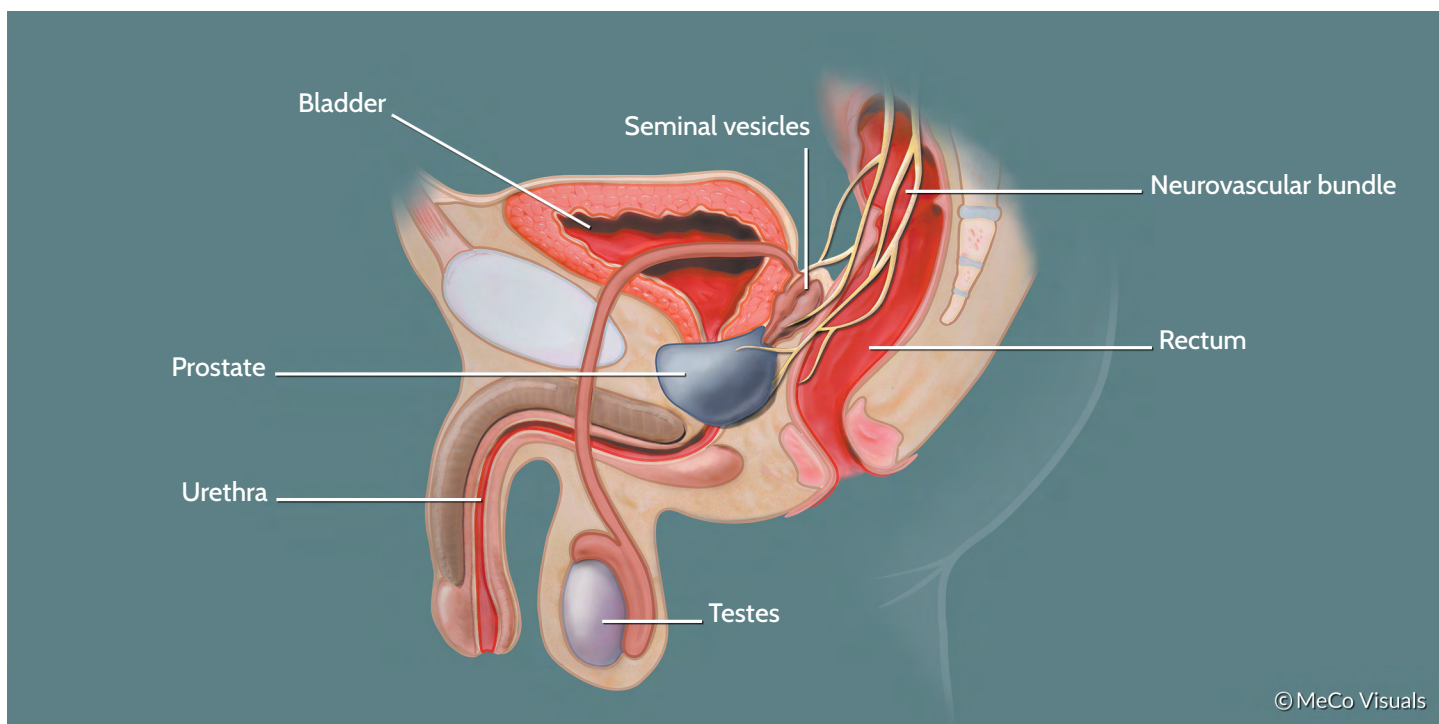
The **bladder** gets larger as it fills up, like a balloon, holding urine until the body is ready to void. The **urethra**, a narrow tube that connects to the bladder, runs through the middle of the prostate and along the length of the penis, carrying both urine and semen out of the body. It is the hose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

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

The Biology of Prostate Cancer

To understand diagnosis and treatment options, it is important to understand how prostate cancer grows. A normal prostate processes **androgens** (hormones such as testosterone) as part of its everyday function.

Prostate Anatomy



© MeCo Visuals

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

Understanding Metastasis

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

Metastasis refers to tumor cells leaving the primary cancer site and forming tumors somewhere else in the body.

If and when prostate cancer cells gain access to the lymphatic system, they can be deposited in various sites throughout the body. Prostate cancer cells can also gain access to the bloodstream and deposit at various sites, most commonly in bones, and sometimes in other organs such as the liver or lungs. Even cancer that initially appears confined to the prostate may have spread. Studies using newer types of molecular imaging (for example, a PSMA PET scan—see page 16) show that a substantial proportion of patients who were initially thought to have localized prostate cancer actually have small deposits of metastatic disease.

What is PSA?

PSA, or Prostate Specific Antigen, is a protein enzyme 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 check for prostate cancer. When there is a problem with the prostate—such as the development and growth of prostate cancer—more PSA can be released. PSA eventually reaches a level where it can be easily detected in the blood. This can be the first indicator of prostate cancer.

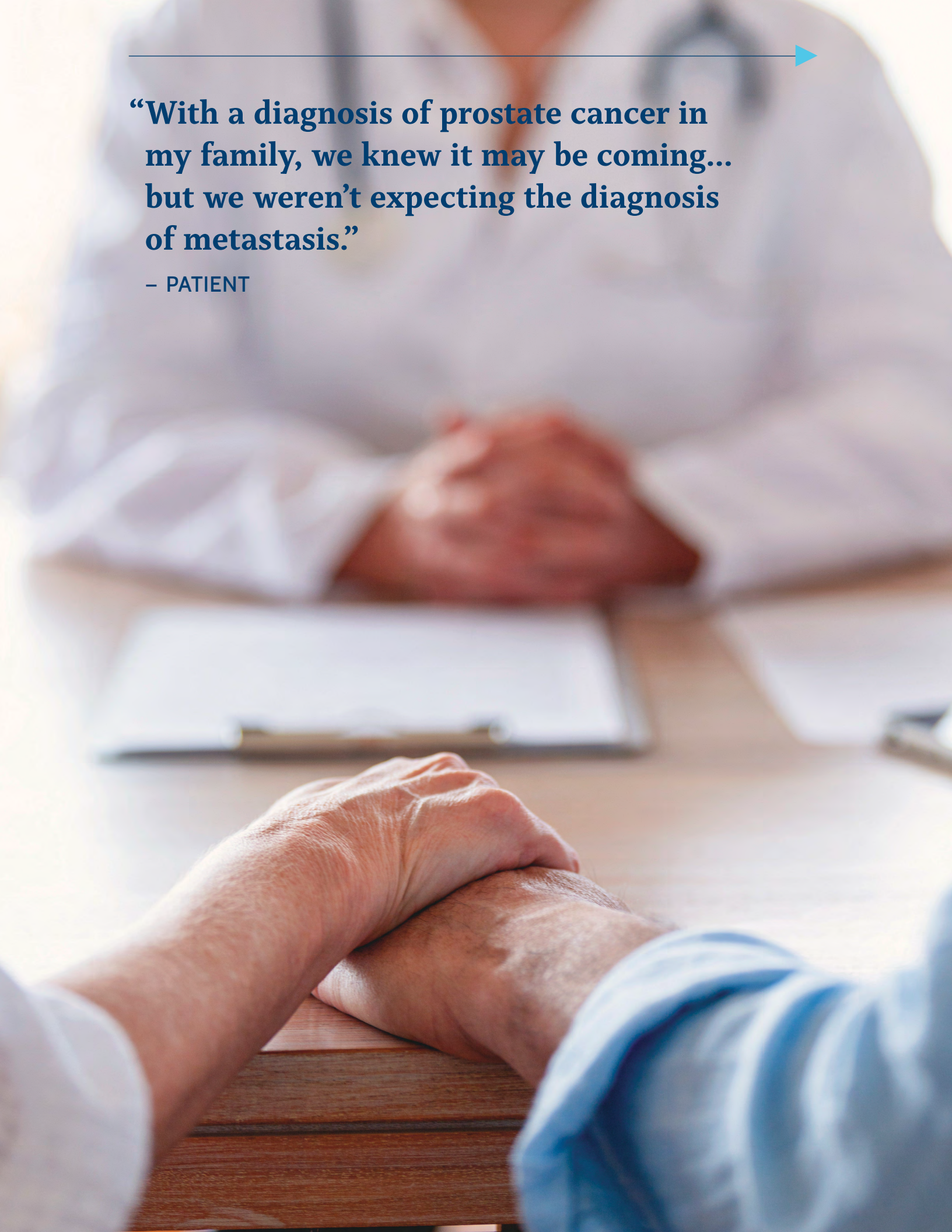
Q: If my doctor tells me that I have prostate cancer metastases in my bones or my lungs, does that mean I have bone cancer or lung cancer?"

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.

PSA testing is the current test of choice for prostate cancer screening. (Go to pcf.org for more information on prostate cancer screening.) During a PSA test, a small amount of blood is drawn from a vein (usually in the arm), and the level of PSA in the blood is measured. Doctors look at the PSA level over time, comparing it with prior test results, and consider whether there could be a benign (non-cancer) explanation for a rising PSA. (Other causes include prostate inflammation, benign prostate enlargement, or a urinary tract infection.) As the PSA number goes up, the chance that cancer is present increases.

Historically, men whose levels are confirmed to be over 4 ng/mL are often recommended to undergo further testing in the form of imaging and/or genetic tests, often with a prostate biopsy. However, this PSA "cutoff" differs from one individual to the next. This level does not necessarily mean that prostate cancer is definitely present, and, conversely, some cancers may be present even when levels are lower, particularly among younger men. It is important to highlight that the PSA test in this setting is a screening, not a diagnostic, test. Your physician will need to perform a prostate biopsy to confirm the presence or absence of prostate cancer.

PSA testing is also used after treatment for prostate cancer to monitor for disease recurrence, and to assess how the cancer is responding in patients undergoing treatment for advanced disease (see Chapter 4.)

A photograph showing a doctor in a white coat sitting at a desk with a clipboard. In the foreground, a patient's hands are clasped together on the desk. The background is softly blurred, focusing attention on the hands and the text overlay.

“With a diagnosis of prostate cancer in my family, we knew it may be coming... but we weren’t expecting the diagnosis of metastasis.”

– PATIENT

UNDERSTANDING YOUR DIAGNOSIS

A diagnosis of prostate cancer can be confusing, frightening, and overwhelming. Whether you are a newly diagnosed patient, or are facing a potential recurrence, you might be torn between arguments favoring one treatment plan over another, or you may feel ill-equipped to make the decisions required of you. 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 empowered to make an informed decision, appropriate for you and your family.

DETECTION: INTERPRETING THE PSA

A blood test for PSA can be used to detect prostate cancer when no symptoms are present. It can help catch the disease at an early stage when treatment is thought to be more effective and potentially has fewer side effects. During a PSA test, a small amount of blood is drawn from the arm, and the level of PSA is measured. (Read more about PSA screening on page 9.)

After your PSA test, your health care provider may perform a digital rectal exam (DRE), in which a lubricated, gloved finger is inserted into the rectum to examine the prostate for any irregularities in size, shape, and texture, as well as to assess for tenderness. Note that the DRE cannot feel prostate abnormalities in the anterior (forward) area of the prostate, away from the rectum, and is often most useful only when the prostate cancer has grown sufficiently to cause cancer that can be felt with a finger.

Your doctor will consider several factors when evaluating your PSA level, including age and other prostate conditions.

Historically, many physicians used a PSA level of 3 or 4 ng/mL as the borderline between “normal” and “abnormal.” We now realize that this assessment is more complicated, and a high PSA does not always mean cancer. A high PSA may be due to an underlying infection, prostate growth, inflammation of the prostate, or another benign cause. PSA increases with age, and your PSA should be compared with normal values for men in your age group. For example, the average PSA for younger men (aged 40–49) ranges from 0.5–0.7 ng/mL, and men with a PSA above the median are at higher risk of later developing prostate cancer. However, it is important to understand that a PSA above 3 or 4 ng/mL may suggest the need for further testing, such as imaging, other blood tests, or a biopsy.

Although a high PSA may increase a doctor’s suspicion of prostate cancer, a biopsy is necessary to confirm a diagnosis.

A small but important proportion of men are at increased risk of prostate cancer due to them carrying an inherited cancer risk gene mutation (e.g., *BRCA2*) or having a strong family history of cancer. People with at least one first-degree relative (such as a father or brother) who had or has prostate cancer may start PSA screening earlier. You should ask your doctor about this, if you are concerned.

In rare cases, men who have a very low 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. Your urologist will consider your PSA levels in light of all of these factors.



Newer studies show that performing an MRI prior to a 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.

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 can be used to assess whether you should have further testing—usually in the form of imaging and/or a biopsy to determine the presence of cancer. Commercially available blood and urine tests may provide additional information, helping you and your doctor determine whether a benign condition may be at play, or whether a biopsy is warranted. These include free PSA, Prostate Health Index, 4KScore®, EPI test, PCA3, MyProstateScore™, and Select MDx®. These tests may be useful in select cases; however, routine use in every patient is not currently recommended by clinical guidelines. Some of these tests may also be combined with magnetic resonance imaging (MRI).

HOW MRI SCANS MAY BE USED IN AIDING DIAGNOSIS

MRI may be used in two main ways when a man is found to have an elevated PSA:

- ▶ Help determine if a biopsy is needed
- ▶ Help direct location of biopsy needle sampling to maximize detection of clinically-significant prostate cancer in patients for whom a biopsy is clinically indicated

MRI can highlight suspicious areas, indicating the potential presence of cancerous lesions and helping to determine whether a biopsy is needed. PI-RADS (Prostate Imaging Reporting and Data System) is a structured reporting rubric to evaluate for the likelihood of clinically-significant prostate cancer based on an MRI scan. The scores range from 1 (very low/clinically significant cancer is highly unlikely to be present) to 5 (very high/clinically significant cancer is highly likely to be present). PI-RADS 4 or 5 lesions have a high probability of harboring clinically significant disease and typically warrant targeted biopsy for confirmation.

If it is determined that a biopsy is recommended, MRI-“targeted” or “fusion” biopsies are increasingly being offered at select centers. This procedure uses 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 is why it matters: MRI technology is like fine photography. Just as excellent photographers will put the subject in focus and the background out of focus, this should happen with an MRI as well. The value or accuracy of prostate MRI and PI-RADS can be dependent on the MRI machine and the experience of the radiologist.

If possible, MRI and fusion biopsy should be performed and interpreted at a high-volume center with particular expertise in prostate MRI. Research for the improvement of this technology continues.

There are three main ways men are initially diagnosed:

1. TRUS-guided biopsy: A transrectal ultrasound-guided (TRUS) biopsy using local anesthetic is currently the most commonly used biopsy technique 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. If a patient had an MRI before the biopsy, needles may be directed into areas that looked suspicious on the MRI. (The MRI itself provides useful information but cannot currently diagnose prostate cancer.)

2. Transperineal biopsy: The prostate can also be biopsied under local or general anesthetic by placing needles through the skin between the scrotum and anus (perineum). An ultrasound probe is still placed in the rectum, as this allows for visualization of the prostate. However, as opposed to transrectal biopsies, the needles are directed through the perineal skin and not through the rectum. This method has a theoretical lower risk of infection, as biopsy needles are not directly contaminated by feces. To date, however, this potential benefit has not been confirmed by data from clinical

trials. While not yet widely used in the U.S., it is expected to become more commonly available.

Both of these methods of biopsy have some inherent risks of infection, bleeding, and pain. You may see blood in your urine, semen, or feces. This typically resolves within 7 days; however, blood in the semen may last for up to 6 weeks. Some men may experience temporary difficulty having an erection and/or an increased difficulty with urination after their prostate biopsy.

3. Incidentally: Some men are diagnosed when prostate cancer is found incidentally during an unrelated surgical procedure of the prostate or bladder (e.g., a TURP: scraping of the prostate for men with difficulty urinating due to benign prostatic hyperplasia).

The tissue samples taken during the biopsy are examined under a microscope by a pathologist to determine whether prostate cancer cells are present, and, if so, how abnormal and aggressive they appear. This is the **grade** of your prostate cancer (see page 14).

TALKING WITH YOUR INSURANCE PROVIDER

Health care systems are sometimes slow to make advances in diagnosis and treatment accessible and affordable to all. It is important to speak with your insurance company directly about what is needed. Find out if there is a staff member who specializes in cancer-related insurance claims.

If you need to talk to your insurance company about paying for a procedure that they consider to be outside the standard of care, it is important to be ready to provide the reasons why this test or procedure is critical for your health. Some tests may actually reduce overall costs if used in the appropriate setting by removing the need for later, unnecessary tests. In other words, when speaking to insurance, make sure to speak their language.

Let us take MRI fusion biopsy as an example. There is evidence that performing an MRI prior to prostate biopsy is useful for assessing risk and allows targeting of the biopsy in patients with suspected prostate cancer. 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.

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. What is FDA-approved (or recommended by expert guidelines) vs. what is covered by insurance is constantly changing. It is important to be an informed patient and to advocate for yourself.

STAGING: HOW SERIOUS IS MY PROSTATE CANCER?

A cancer's "stage" describes where in the body the cancer exists or has spread. Scans to determine the stage is called **staging**. The goal of staging your cancer is to provide an estimate of your prognosis (the likely course and outcome) 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. "Risk groups" have been the most common method to describe a patient's prognosis for cancer that is localized (confined to the prostate). (Risk groups and their treatment options are not described in detail here; see PCF's *Patient Guide to Localized Prostate Cancer*.) If you have been diagnosed with metastatic disease (that has spread beyond the prostate), you may hear this described as "Stage 4 prostate cancer."

There are 5 main components to risk-stratifying prostate cancer:

Your PSA level	When performed pre-diagnosis: How likely is it that you have prostate cancer? When performed post-diagnosis: How likely is it that your cancer has spread beyond the prostate?
The grade of your tumor (done via biopsy)	How aggressive is your cancer? Grade refers to how "abnormal" cells look under the microscope, with higher grade referring to more "abnormal" looking cells and, thus, more aggressive disease.
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 worse than a cancer found in just 2 of the cores.
The T-stage of your tumor	For example, is the prostate cancer contained completely within the prostate?
The spread of the cancer	Based on imaging, has the cancer spread to lymph nodes (termed the "N-stage" for nodes) or bones or other organs (termed the "M-stage" for metastasis).

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 newer 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 level and dividing it by the volume (size) of your prostate in grams or milliliters. PSAD values of 0.15 or greater (e.g., a PSA of 7.5 or above for a 50-mL prostate) may be concerning.

2. Grade: How aggressive is the cancer?

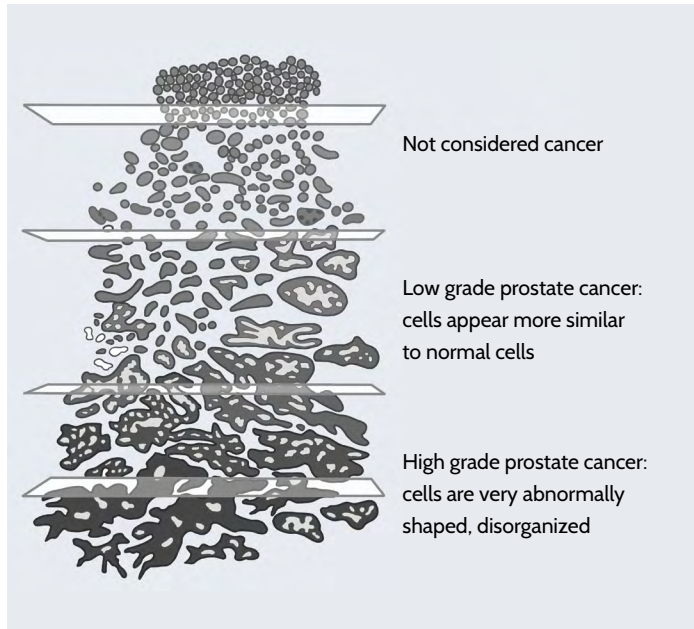
If prostate cancer is found when looking at biopsy tissue under a microscope, the pathologist assigns a grade to the cancer. There are 2 grading systems, which can be confusing for patients.

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). The newer Grade Group system ranges 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 Gleason score.

Gleason Score and Grade Group Comparison

Gleason Score	Grade Group
Gleason Score 6	Grade Group 1
Gleason Score 7 (3+4)	Grade Group 2
Gleason Score 7 (4+3)	Grade Group 3
Gleason Score 8	Grade Group 4
Gleason Score 9-10	Grade Group 5

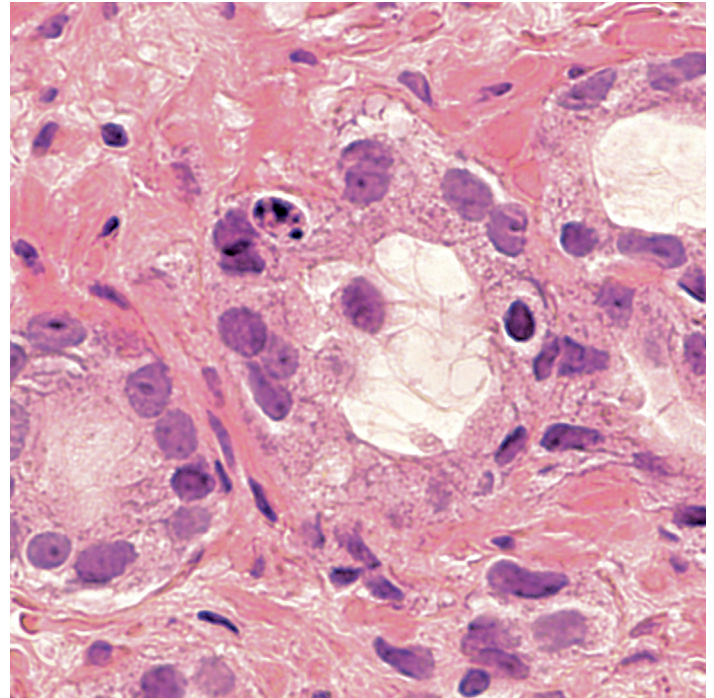
How Pathologists Consider Gleason Patterns



3. Biopsy cores: How many were positive?

In addition to the grade of your cancer, your physician will consider the percentage of 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 may be. For example, if 12 biopsy cores were taken, and 9 were involved with cancer, then you would have 9/12, or 75% positive cores.

Your doctor will use information from several sources to characterize your prostate cancer, including your PSA level, physical exam, biopsy results, and imaging.



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

SIZE VS. GRADE

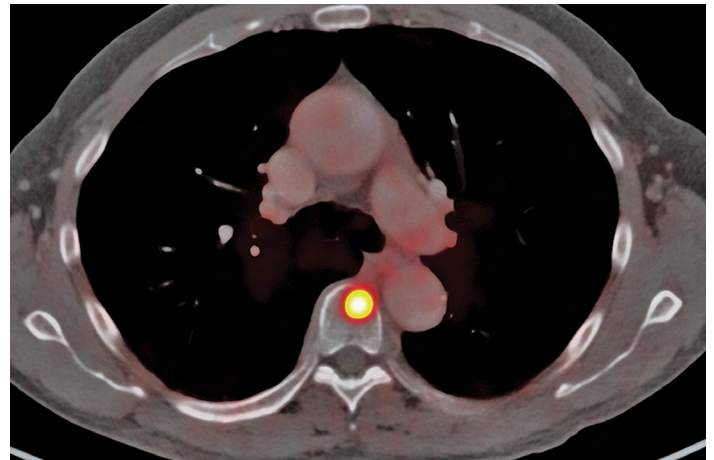
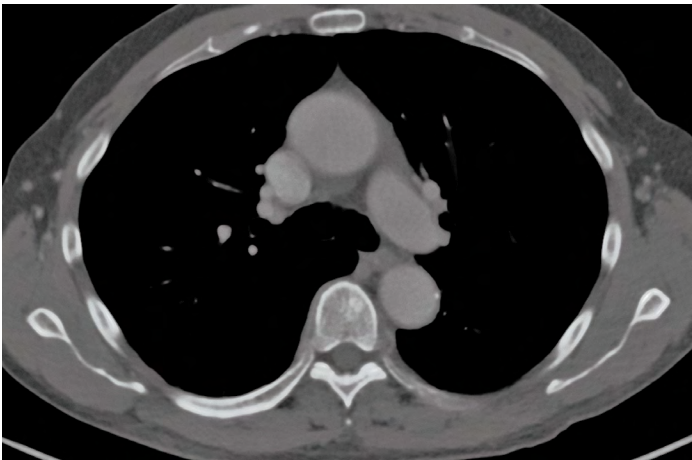
The size and grade of your tumor do not always predict its behavior over time. A small, high-grade cancer is much more likely to spread to other parts of the body than a large, low-grade cancer. In some cases, tests of your tumor's genetic material and/or proteins may be better predictors of growth over time (see page 18). Consult with your healthcare provider to find out if further testing might be right for you.

PSMA PET IMAGING

PSMA PET is a newer, highly sensitive imaging scan that can detect prostate cancer metastases much earlier, when they are much smaller. It 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 were previously treated for prostate cancer (usually with surgery or radiation therapy) and now have a suspected recurrence, based on elevated PSA levels.

How does it work? PSMA, short for Prostate Specific Membrane Antigen, is a protein found on the surface of prostate cancer cells. The “imaging agent” consists of a chemical that binds to PSMA, homing 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, “tagging” prostate cancer cells. The patients are then scanned with an imaging camera that detects where cells “light up” in areas where the molecule has accumulated—i.e., sites of prostate cancer (see photo below). It is important to know that PSMA also exists to some degree in non-prostate tissues, including in the liver, kidneys, some glands in the head and neck, and the small bowel. These areas will “light up” also. Should you see this on your scan report, it does not necessarily indicate cancer in these areas.

PSMA PET imaging may help guide your treatment plan. Researchers continue to study how best to use this technology to improve patient outcomes.



Left: A traditional CT scan does not clearly show metastasis in the spine.

Right: In the “fused” PSMA PET/CT image, the prostate cancer metastasis “lights up.”

4. Tumor staging (T-stage): The local extent of the prostate cancer

The digital rectal exam (DRE) gives information on how extensive the prostate cancer is within the area of the prostate reachable in that exam. If there is suspicion that the cancer extends outside the prostate, your doctor may order a prostate MRI (which is more accurate for staging than a DRE).

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
- ▶ T2: The health care provider felt a nodule(s) on your prostate during the rectal exam, or the cancer was seen on imaging (ultrasound or MRI of the prostate)
- ▶ T3: The tumor extends out of the prostate capsule, possibly including the seminal vesicles
- ▶ T4: The tumor has invaded the rectum, bladder, penis, or pelvic side wall (advanced)

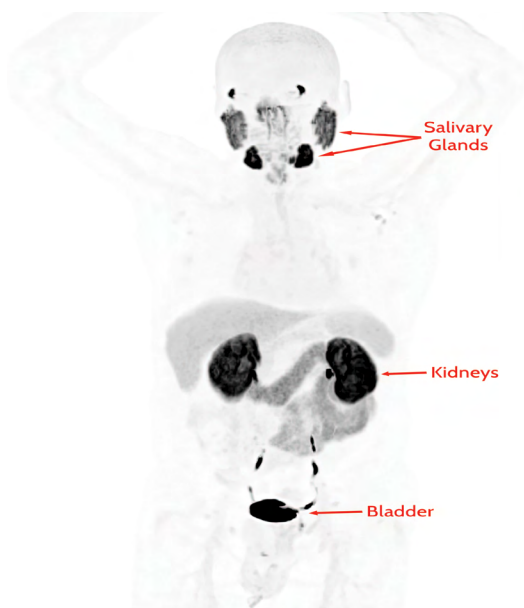
5. Evaluating for metastatic disease: Has the tumor spread beyond the region around the prostate?

Aggressive cancers (e.g., PSA greater than 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 include molecular positron emission tomography (PET) imaging, such as PSMA PET (see box on the previous page). Ask your doctor what type of imaging would be right for you.

It is important for your doctor to know if your cancer has spread to lymph nodes, bones, or other body sites, since that will influence their treatment recommendations.

Knowing the risk features and extent of spread of your cancer provides information about your prognosis (the likely course and outcome) and treatment options.

Imaging Scans are Used to Evaluate for Metastasis



Note that uptake to the salivary glands is normal, since PSMA is expressed there. Also note that the contrast is emptied through the kidneys and bladder, and this is also normal. See arrows in image at left.

Left: A patient's PSMA PET scan shows no metastases.

Right: A patient's PSMA PET scan shows extensive metastases to the bones, lymph nodes, and lining of the abdomen (peritoneum).

A Closer Look: Newer Tests of Genes and Proteins

Doctors have been able to see cancer under a microscope and on imaging scans for decades. Today, newer tests can look at features that are millions of times smaller: the genetic material of your biopsy tissue or of your blood, saliva, or urine. This deeper look may provide additional information to help guide your treatment plan, or to inform your family members' risk for cancer. If you have been diagnosed with metastatic prostate cancer, it is especially important to talk to your doctor about referral to a genetic counselor.

GENETIC TESTING FOR INHERITED MUTATIONS

Genetic testing for inherited cancer risk uses a sample of your blood or saliva. These tests examine your inherited DNA for changes (called "mutations") that might signal a higher risk for cancer that is passed down through families. This can be true even without a known history of cancer in your family, or with a history of non-prostate cancers. Talk to your doctor about referral to a genetic counselor if you have one or more of the following risk factors:

- ▶ Diagnosis of high-risk, regional, or metastatic prostate cancer
- ▶ Biopsy shows intraductal carcinoma or cribriform pattern (see your pathology report)
- ▶ Blood relative with a known cancer risk gene mutation
- ▶ Strong family history of prostate or other cancers
- ▶ Early age of diagnosis (i.e., younger than 50 years of age)

TUMOR BIOMARKER TESTING

Tests of biopsy tissue examine your prostate tumor's genetic material, gene expression, or proteins (called "biomarkers"). In some situations, these tests help provide further assessment of the aggressiveness of your cancer beyond the Gleason score/Grade Group, PSA, and T-stage, including:

Decipher[®] Prostate Biopsy, Opko 4K,[®] Oncotype DX Prostate,[®] Prolaris,[®] and ArteraAI Prostate Test.[®]

Medicare usually covers the use of these risk-assessment tools, but not all private insurance plans cover them. Ask your physician if these tests would be right for you.

For patients with aggressive or metastatic disease, your doctor may recommend genetic testing for inherited mutations or biomarker testing of your tumor to help determine if there is a targeted therapy for your type of prostate cancer.

ASSEMBLING YOUR TEAM

Decisions about how to treat your prostate cancer cannot be made in a vacuum. A new diagnosis can come with a lot of confusing information and feelings. Yet, even during this chaotic time, you'll be asked to make some important decisions based on your doctors' recommendations. To help you along the way, it is important to seek support from family, friends, and doctors.

Doctors and Practitioners

Where possible, select a physician who specializes not just in cancer, but has experience 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.

Other factors to consider when selecting a doctor:

- ▶ Are they affiliated with a university or research hospital?
- ▶ Did they seem rushed, or do they seem interested in what is important to you?
- ▶ Did they explain all of the treatment options to you?
- ▶ Are you able to communicate with them with ease?
- ▶ Are they covered by your health insurance? If not, can you change insurance?

Remember:

- ▶ Take your time—but not too much time. Advanced prostate cancer requires careful monitoring and, in most cases, treatment with minimal delay
- ▶ Get second or even third opinions if you don't feel comfortable
- ▶ Be careful of advice that seems highly opinionated, e.g., "there is nothing we can do for you" or "eat this herb and your cancer will be cured"



Every patient has different priorities and concerns about quality of life. Ask questions to help you understand and process your diagnosis as well as the therapy options available.

- ▶ Avoid any health care provider who seems like he or she is "selling" something. For accurate information, use reputable websites like pcf.org and those that your doctor recommends
- ▶ Once you have selected a doctor, trust is key. You are partners in this process
- ▶ 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 assist in maintaining the "bigger picture" perspective, taking your overall health into consideration, and can help you work through complicated decisions.



It may be helpful to enlist a family member or friend to act as a health advocate, helping you review and process all the new information.

Friends and 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 seem like a fantastic offer. But after a cancer diagnosis, you may feel confused about how much support to accept, request, or decline. Keeping open channels of communication is key.

Tips for Spouses, Partners, Caregivers, and Adult Children:

- ▶ Agree on how you will make decisions
- ▶ Get ready for changes in routine
- ▶ Ask how treatments may affect moods, physical ability, and body functions

- ▶ Understand that changes can trigger emotions in both the patient and family members
- ▶ 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

With friends and family who have volunteered their assistance, let them know a few specific things that would be helpful. Examples might include rides to treatment, preparing meals, caring for young children, or performing difficult chores. When things feel overwhelming, don't be afraid to reach out for support, but also don't be shy about politely saying “no” to help you don't want, however generous.

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

You

Sadness, fear, anxiety, sleeplessness, and anger are all normal early emotions after receiving a cancer diagnosis. Coping with these emotions is an important part of your treatment and recovery. Seeking professional help, whether from an online community, clergy, a group at your house of worship, a cancer support group, or a private mental health professional is not 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 they can keep their head in the game: it is vital. To join an online support group, please visit pcf.org/support-groups. For more information on counseling resources, visit cancercare.org.

Taking care of your emotional and mental health is a vital part of prostate cancer treatment and recovery.

PAYING FOR CANCER TREATMENT

Undergoing cancer treatment is challenging enough, but it can also be expensive. You may worry about your ability to pay for treatment along with other necessities, like food, housing, and travel. Ask your healthcare provider to direct you to patient advocates and social workers.

Do not let financial constraints deter you from getting the care or treatment you deserve and need.

Here are some resources that may help:

Paying for treatment

- ▶ U.S. government programs include Medicare (for age 65 or older) and Medicaid (depending on your income)
- ▶ Organizations such as CancerCare and the Patient Advocate Foundation offer some direct financial assistance and can help you navigate through insurance and other financial assistance programs
- ▶ Many pharmaceutical companies have treatment assistance programs. Ask your doctor for more information or seek out these companies online
- ▶ Speak with your doctor and hospital's billing department early, so that you do not have unexpected bills. You may be able to arrange a payment plan
- ▶ There may be alternate medicine choices that may be covered differently and/or have a different co-pay. Ask your doctor if this is the case

Housing

- ▶ Your cancer treatment center might be far from home, making it difficult for your family to remain with you. The American Cancer Society Hope Lodge and the Healthcare Hospitality Network provide low-cost or free housing for families of cancer patients
- ▶ Medical bills can put a strain on other costs like mortgage or rent payments. Speak with your bank or landlord to see if they can make accommodations. You can also explore programs for affordable rental housing sponsored by the government
- ▶ If you are a Veteran, check with your local VA about possible resources



Proactively reach out to your insurance company, providers' billing departments, patient advocates, and social workers about available resources.

Travel

- ▶ Mercy Medical Angels provides free medical transportation for patients in need. Your Medicaid office might offer assistance with treatment-related travel

Food

- ▶ The Supplemental Nutrition Assistance Program (SNAP) provides electronic credits to allow families in need to shop for groceries. Go to www.fns.usda.gov/snap to learn more. Feeding America helps families find local food banks

Caregiver expenses

- ▶ Depending on your stage of cancer, type of treatment, and overall health status, you might benefit from having a designated paid caregiver. Contact your local Medicaid office to learn about social services programs that can help you pay for in-home care

TOOL: BUILDING YOUR TEAM

Many medical specialists may be involved in the treatment of your prostate cancer.

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

Urologic Oncologists are also urologists, but who specialize in the treatment of cancers of the urinary tract (kidney, bladder, prostate, testis, 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, and targeted therapies. Your urologic oncologist and/or radiation oncologist may also be equipped to provide systemic therapies, based on their level of expertise.

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.

Sexual Medicine Specialists are clinicians, often urologists, with additional training in sexual and hormonal conditions.

Nurse Practitioners (NPs) and **Physician Associates (PAs)** are advanced practice providers who work closely with physicians to help you with your care. They are often the first line of response for your questions and concerns and also manage some aspects of routine follow-up care. Patients may be assigned a nurse case manager who will be their primary contact with their care team.

Oncology Nurses assist in administering therapies and monitoring your overall health as you progress through your treatment.

Dietitians and Nutritionists counsel patients on nutrition and wellness issues to maximize health during and after treatment.

Naturopathic Doctors support patients with complementary medicine and mind-body awareness related to cancer and treatment.

Physical Therapists create and execute rehabilitation programs to restore function and minimize 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.

Psycho-Oncologists are clinicians with specific training in dealing with the depression, anxiety, and fear related to cancer.

TOOL: QUESTIONS TO ASK YOUR DOCTOR

Men who are diagnosed with metastatic prostate cancer today have options available to them. Here are a few questions to help guide conversations with your treatment team.

Your Cancer:

- ▶ What is my PSA level? If the test has been repeated over time, how fast has it risen, and what does this mean for me?
- ▶ What is my prostate cancer Grade Group? What does this mean in terms of our approach to my treatment?
- ▶ Where has my cancer spread beyond the prostate? What does that mean in terms of my likely course and outcome?
- ▶ Are there additional tests I need to have to gain a more precise understanding of the stage and aggressiveness of my cancer, which may affect subsequent treatment decisions?

Your Treatment Options:

- ▶ What treatment options exist for my cancer? Which treatment do you think is better for me?
- ▶ What would be the benefit of getting a second opinion in terms of treatment options?
- ▶ What other specialists should I see to understand all 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?
- ▶ Should I join a clinical trial?

Side Effects:

- ▶ What side effects can I expect from the treatments available to me? Are the risks different with different treatments?
- ▶ How do my baseline urinary, sexual, or bowel function affect my treatment decisions, if at all?

Other Considerations:

- ▶ How can I improve the success of my therapy? Are there dietary changes I need to make? What about exercise?
- ▶ What can my family learn from my diagnosis? Do they have a higher chance of being diagnosed with cancer, as well?
- ▶ How might my treatment impact the management of my other medical problems, particularly with regard to medications I am already taking?

Remember, you want to be a partner in your own care. The more informed and proactive you are, the better.

If you have been newly diagnosed with metastatic prostate cancer, please see Chapter 4 for information on treatment options. Chapter 3 addresses recurrent prostate cancer.

“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 may be because your cancer cells have previously been removed with surgery or killed with radiation, but your PSA has started to rise again. Why? Some prostate cancer cells might have spread outside the prostate before they could be removed or killed. Over time, these cells may begin to multiply and produce enough PSA to subsequently be detected by lab tests. PSA monitoring after treatment is the main way to track whether all of the cancer cells were destroyed.

If you previously had surgery, ideally your PSA should be undetectable (below the lab's minimal threshold level). If you had radiation therapy, you will have a different low point for your PSA (called a "nadir"). PSA is produced by all prostate cells—not just prostate cancer cells—so patients who have had radiation therapy may have normal prostate cells that still make PSA. 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. 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. Some doctors may have a lower threshold of concern (as low as 0.1 ng/mL). This will depend on factors such as surgical pathology findings and PSA velocity.

Radiation Therapy Patients: If your PSA is 2.0 ng/mL greater than your lowest reading after treatment (referred to as your "nadir" reading), as measured on 2 consecutive tests.

PSA DOUBLING TIME

The rate at which your PSA rises (and how quickly it doubles) after prostatectomy or radiation therapy is one signal of how aggressive your cancer is and can be useful for determining how aggressively it may need to be treated.

Research has shown that patients whose PSA doubled in under 6 months (fast) had the most aggressive tumors and were more likely to die from their disease, whereas those with longer PSA doubling times have less aggressive tumors and are less likely to die from their disease.

A shorter PSA doubling time indicates more aggressive disease.

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. Newer, more sensitive scans (such as a PSMA PET scan, see page 16) can detect very small areas of cancer, when the PSA level is lower. These are rapidly becoming a "gold standard" to evaluate rising PSA after initial treatment, and are increasingly available at centers across the U.S. Now that doctors can "see" cancers much earlier than with traditional types of imaging, research is ongoing to understand how best to use these scans to inform when and how to begin treatment. Ask your doctor what type of imaging would be right for you.

Your test results may show that your cancer has recurred "locally" or "locoregionally," meaning in or near the prostate region, or is "metastatic," meaning that it has recurred outside the prostate area. Imaging scans may also show no cancer. This is called **biochemical recurrence**, meaning that the only evidence of cancer recurring is a laboratory value—a rising PSA.

Whether your cancer has recurred locally OR has metastasized, you have many treatment options to discuss with your doctor.

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 often 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 radiation oncologist or medical oncologist to my treatment team to gain an additional perspective on treating my disease?
- ▶ If you recommend that I initiate 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? For how long will I need it?
- ▶ Should my treatment plan also include androgen receptor pathway inhibitor 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?

ADDRESSING BIOCHEMICAL RECURRENCE

If you are experiencing biochemical recurrence, your doctor will consider your PSA doubling time and other factors in determining whether and when to initiate treatment. Recall that this means you have no spots of cancer on scans, either in the prostate area or elsewhere in the body.

Patients with a rapidly rising PSA (doubling time of approximately 9 months or less) can be considered to have “high risk biochemical recurrence.” They are at greater risk for developing metastases and for death from prostate cancer. One treatment option is enzalutamide, an androgen receptor pathway inhibitor (see Chapter 4). This medicine can be given with or without another medicine, a type of hormone therapy called a GnRH analog. Talk to your doctor about your risk of cancer progression and whether starting treatment would be right for you.

THERAPIES FOR LOCALLY RECURRENT PROSTATE CANCER

If PSA starts to rise after surgery or radiation therapy, your doctor may determine that the cancer is local, meaning in or near the prostate. In this case, re-treating the prostate area may provide a second chance at cure. This is called **salvage therapy**. Whether your initial treatment was radiation therapy or surgery, you can discuss salvage options with your treatment team (see chart on the next page). In some cases, hormone therapy will be combined with radiation therapy.

Since this is essentially a cumulative treatment beyond your initial treatment, there is a risk of increased side effects. These include rectal bleeding, incontinence (urinary leakage), strictures and difficulty urinating, diarrhea, erectile dysfunction, and fatigue. Be sure to discuss potential side effects with your doctors before deciding on a course of therapy, but don't delay; addressing side effects may be better than risking disease spread.

Salvage Therapy Options After Recurrence

If your initial treatment was surgery, your salvage treatment can be:	If your initial treatment was radiation therapy, your salvage treatment can be:
Radiation therapy with or without hormone therapy	Further radiation with SBRT or brachytherapy with or without hormone therapy OR Cryotherapy OR Prostatectomy
Radiation therapy uses external beams of high-energy radiation to kill cancer cells. Patients come to the treatment center each weekday for 4–6 weeks.	
SBRT (Stereotactic body radiation therapy): A subtype of radiation therapy that uses higher radiation doses per day over a short timeframe (about 5 days).	
Brachytherapy: Radiation therapy “seeds” or catheters (small tubes) are placed inside the prostate. This is internal, rather than external, radiation therapy.	
Cryotherapy: Prostate cancer cells are frozen to death via probes inserted into the prostate through the perineum (between the scrotum and anus).	
Hormone Therapy: Medicines that work throughout the body to lower testosterone or block its effects, slowing or stopping prostate cancer growth (see Chapter 4).	

In particular, salvage prostatectomy appears to carry a significant risk of side effects, including urinary incontinence, rectal injury, and erectile dysfunction. This option should only be considered in discussion with a urologic surgeon who has extensive experience with this procedure in the salvage setting.

A NOTE ON SIDE EFFECTS

While it is important to know about all of the possible side effects, keep in mind that they can also be managed. Urinary leakage can be managed without surgery (with various types of urine collection systems) or with a surgical procedure such as placement of a sling or artificial urinary sphincter. Options for erectile dysfunction include oral medications, injections, a vacuum pump, or a penile implant. You may need to see a specialist for help with certain side effects; your urologist may not have formal training in these areas.

TIMING OF SALVAGE RADIATION AND USE OF HORMONE THERAPY

The best time to receive salvage radiation therapy following radical prostatectomy is when your PSA first becomes detectable again, ideally when it is 0.2 ng/mL or less, and definitely below 0.5 ng/mL if possible.

Another approach is to give radiation therapy upfront, or “prophylactically,” after surgery, without evidence of cancer recurrence (i.e., without a rise in PSA). This is called **adjuvant radiation therapy**. However, research shows that waiting to give radiation therapy until the PSA becomes detectable (i.e., PSA of 0.1–0.15 ng/mL) results in similar outcomes for the majority of patients with biochemical recurrence. This is termed **early salvage radiation**.

Your physician may recommend the use of hormone therapy along with your salvage radiation therapy. There is evidence that use of 2 years of hormone therapy in this setting may delay the development of metastasis. This shared decision will be made in conjunction with your treating physician and will depend on many factors, including your PSA level, surgical pathology report, and imaging findings.

In some patients, the PSA may be coming from prostate cancer cells outside the prostate area. Those patients are less likely to benefit from additional local therapy. The next section discusses how to treat prostate cancer that has spread into other areas of the body.

“My attitude has always been positive. I stay informed about research. There’s more coming down the pike all the time.”

– PATIENT



WHAT IS METASTATIC PROSTATE CANCER?

Metastatic prostate cancer refers to cancer that has spread beyond the prostate to other parts of the body. Prostate cancer most commonly spreads to lymph nodes and bones, and sometimes to other organs such as the liver or lungs. You may also hear this described as **advanced prostate cancer**. Patients can have metastatic prostate cancer at the time of initial diagnosis, or they may have metastases as a recurrence of their disease, years after treatment for localized prostate cancer.

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

Treatment of metastatic prostate cancer is generally based on whether its growth can be slowed or stopped with **hormone therapy**. Recall that testosterone (an androgen hormone) is the “fuel” that makes prostate cancer cells grow (see [The Biology of Prostate Cancer, page 8](#)). 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 a part of most treatment plans for advanced and metastatic prostate cancer. Prostate cancer that can be controlled by hormone therapy is called **hormone-sensitive prostate cancer (HSPC)**.

However, in many patients, some prostate cancer cells eventually gain the ability to grow in the low-testosterone (“castrate”) environment created by hormone therapy. As these hormone therapy-resistant prostate cancer cells continue to grow, standard hormone therapy 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 hormone therapy is referred to as **castration-resistant prostate cancer (CRPC)**.

This chapter covers treatment options for hormone-sensitive and for castration-resistant prostate cancer.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (mHSPC)

As noted, hormone therapy is a mainstay of treatment for mHSPC, and, today, is almost always combined with other therapies.

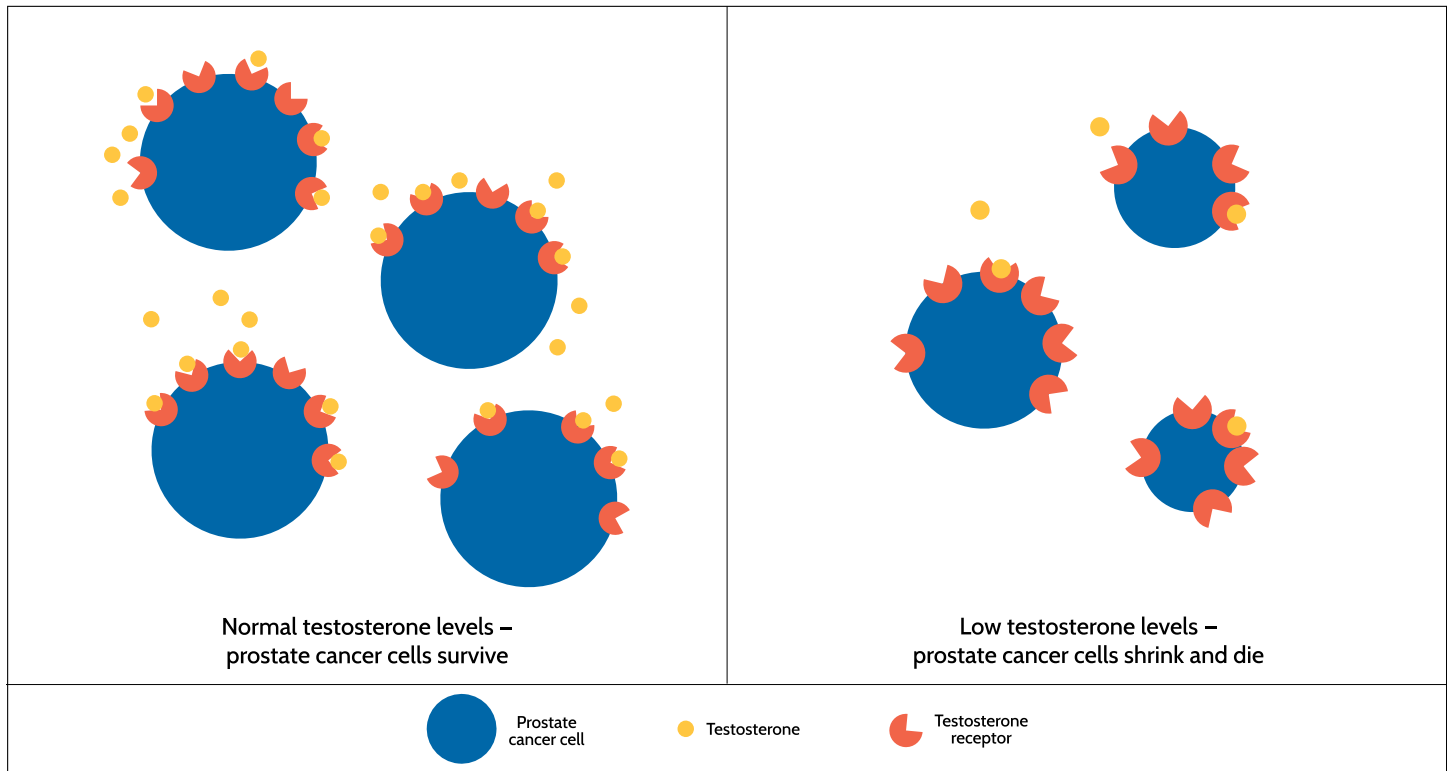
About Hormone Therapy

Hormone therapy is designed to inhibit testosterone production or directly block it from acting on prostate cancer cells. It is, essentially, “anti-testosterone therapy.” The majority of prostate cancer cells will stop growing following the removal of testosterone, and many will die.

There are different forms of hormone therapy that work in different ways in your body. Most are given as regular injections, sometimes in combinations. These forms of hormone therapy have been used for decades. There are also newer **androgen receptor pathway inhibitors** for patients with certain types of advanced prostate cancer (see [box on page 30](#)).

Surgery to remove the testicles (called **orchiectomy**) is another option. About 90% of testosterone is produced by the testicles. The procedure is typically done in the operating room as an outpatient procedure, with the majority of patients being discharged from the hospital on the same day. This is an option for men who prefer a low-cost, one-time procedure. Because it is irreversible, most patients opt for medical therapy.

How Hormone Therapy Affects Prostate Cancer Cells



The chart below lists different types of hormone therapy.

TYPES OF HORMONE THERAPY		
<p>Standard hormone therapy</p> <p>Lower testosterone levels</p> <ul style="list-style-type: none"> Orchiectomy LHRH agonists, e.g., leuprolide (Lupron®, Eligard®) LHRH antagonists, degarelix (Firmagon®), relugolix (Orgovyx®) 	<p>Anti-androgens</p> <p>Help block the action of testosterone</p> <p>Include:</p> <ul style="list-style-type: none"> Bicalutamide (Casodex®) Flutamide (Eulexin®) Nilutamide (Nilandron®) 	<p>Androgen receptor pathway inhibitors</p> <p>Newer medications approved for men with certain states of advanced prostate cancer</p> <ul style="list-style-type: none"> Abiraterone (Zytiga®, Yonsa®) Apalutamide (Erleada®) Darolutamide (Nubeqa®) Enzalutamide (Xtandi®)
<p>LHRH Agonists: These medications work by acting on the release of LHRH, one of the key hormones that initiates the production of testosterone. They are given as regular shots: once a month, or once every 3, 4, or 6 months. LHRH agonists cause a “testosterone flare” reaction, which is an initial, temporary rise in testosterone and can cause a variety of symptoms. It can be prevented by co-treatment with a short course of anti-androgens.</p> <p>LHRH Antagonists: These medications block LHRH from stimulating testosterone production without causing an initial testosterone surge. Relugolix is a newer, oral form with a faster mechanism of action.</p> <p>Anti-Androgens: These drugs can help block the action of testosterone in prostate cancer cells. They are often given concurrently with some hormone injections to prevent symptoms/side effects of a testosterone flare.</p> <p>Androgen Receptor Pathway Inhibitors: Also referred to as androgen receptor signaling inhibitors (ARSIs) or androgen receptor axis targeted agents (ARATs). Abiraterone blocks the production of testosterone, while apalutamide, darolutamide, and enzalutamide block the action of testosterone. These newer “second-generation” hormone treatments are FDA-approved for patients with certain states of advanced prostate cancer: high-risk biochemical recurrence (non-metastatic HSPC), mHSPC, non-metastatic castration-resistant prostate cancer (nmCRPC), and mCRPC. All are taken orally. Some are approved to be given in combination with other medicines.</p> <p>All of these medications have side effects. See Hormone Therapy Side Effects, page 32 for more information.</p>		

WHAT ABOUT PROSTATECTOMY?

Surgery (radical prostatectomy) is currently not recommended for treating metastatic prostate cancer, as it would likely not be curative (because the cancer has already spread) at the cost of possible side effects such as urinary incontinence and erectile dysfunction. However, if the cancer itself is causing significant local symptoms, such as difficulty urinating, surgical procedures such as a transurethral resection of the prostate (TURP) may be considered.

Combination Treatments

Previously, androgen receptor pathway inhibitors (such as abiraterone and enzalutamide), as well as taxane chemotherapy, had been used only after cancer becomes metastatic and resistant to hormone therapy (see [Metastatic Castration-Resistant Prostate Cancer](#) on page 34 for more information). Since then, clinical trials have shown that for patients with mHSPC, adding an androgen receptor pathway inhibitor with or without docetaxel chemotherapy together with standard hormone therapy significantly extended the length of time before disease progression and improved survival. While hormone therapy alone might still be the best choice for a small number of select patients, it is now recommended that patients with mHSPC strongly consider combination therapy with hormone therapy. These options are discussed below.

Hormone therapy plus androgen receptor pathway inhibitor (ARPI): ARPIs (abiraterone, apalutamide, darolutamide, and enzalutamide) are newer types of medicines that block the androgen receptor or block the production of androgens. They can be used in combination with standard hormone therapy for patients with mHSPC. Multiple large randomized controlled clinical trials have shown that this combination approach lengthens patient survival—a 30% to 40% reduction in the risk of death.



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

Hormone therapy plus ARPI plus docetaxel: Adding docetaxel chemotherapy to hormone therapy + an ARPI can be an option for select patients. You may hear this referred to as “triplet” therapy. Consult your doctor as to whether this approach might be right for you.

Treatment of mHSPC is rapidly evolving. Today, the standard of care for most patients is to add other medicines to standard hormone therapy.



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

CAN I TAKE A BREAK FROM HORMONE THERAPY?

Intermittent hormone therapy may allow select patients to stop hormone therapy for a period of time, then restart. Patients report that their quality of life improves as their testosterone levels increase. There may be a trade-off in terms of overall cancer outcome. The most common approach 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. If you are considering this approach, discuss the risks and benefits with your doctor.

So how should patients with mHSPC work with their doctor to choose a treatment plan? The decision to add other treatments to a hormone therapy regimen, and specifically which treatment(s) to add, will be based on clinical factors, such as whether there is a high or low volume of metastatic disease and timing of metastases (i.e., at presentation vs. following a recurrence). Talk to your doctor about whether radiation therapy, and/or an androgen receptor pathway inhibitor with or without docetaxel may be options for you. Consider benefits, risks, side effects, costs, and other health issues.

Remember: For people with mHSPC, combination treatment (beyond hormone therapy alone) is now the standard of care.

Hormone Therapy Side Effects

Testosterone is a hormone that plays an important role in establishing and maintaining characteristics associated with biological males, such as body hair growth, muscle mass, sexual desire, and erectile function. It contributes to a host of other normal processes in the body. Hormone therapy lowers testosterone and causes side effects related to low testosterone.

Hormone therapy plus radiation therapy: For patients with a low volume of metastatic disease at diagnosis, who have not previously received hormone therapy, guidelines now recommend that radiation therapy to the prostate be considered in addition to systemic medical therapy. This benefit was not seen among patients with a high disease burden at diagnosis.

WHAT IF I HAVE JUST A FEW SPOTS OF CANCER?

Some patients have a low number of metastatic lesions seen on imaging, termed “oligometastatic” disease. The threshold is generally 5 or fewer metastatic tumors. Stereotactic body radiation therapy (SBRT), a short course of high-intensity radiation therapy, can be directed to the metastases, and has been shown to delay the time to hormone therapy.

It is important to understand how and why these side effects occur, so you can minimize their impact on your daily life. Although most patients may experience only a few of these symptoms, the list of potential effects of testosterone loss is extensive: hot flashes, decreased sexual desire, loss of bone density and increased fracture risk (osteoporosis), erectile dysfunction, fatigue, increased risks of diabetes, stroke, and heart attacks, weight gain, decreased muscle mass, anemia, mood changes, 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 potential link between prolonged hormone therapy use and increased risk of dementia.

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

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 patient with advanced prostate cancer, it is important to think about ways to prevent, reverse, or identify these effects so that patients can maximize their quality of life.

Certain lifestyle changes, such as related to diet and exercise, have been shown to relieve some of the side effects of hormone therapy (see Chapter 5). Before beginning treatment, discuss these with your doctor and nutritionist, so you can alter your lifestyle to accommodate or head off the changes. Ask your doctor about the increased risk of diabetes, heart disease, stroke, weight gain, high cholesterol, and osteoporosis so that you can undergo screening and, if necessary, treatment for these other conditions throughout the course of treatment for prostate cancer.



Reducing red meat and increasing consumption of brightly-colored vegetables can help during treatment with hormone therapy and beyond.

Side Effects of Androgen Receptor Pathway Inhibitors

Androgen receptor pathway inhibitors (abiraterone, apalutamide, enzalutamide, and darolutamide) are newer medicines that are used for advanced prostate cancer, including now in its initial management. They each have their own safety profile, including side effects and interactions with other medications.

You and your doctor will need to consider your prostate cancer as well as any other medical conditions when choosing among these agents. For example, patients who have cardiovascular disease should be monitored closely when using these therapies and may need to be followed by a cardiologist.

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (nmCRPC)

Some patients who are taking hormone therapy may see their PSA levels rise (meaning that cancer is developing resistance to hormone therapy), but conventional imaging scans (e.g., CT/MRI and bone scan) do not show any sites of prostate cancer. This is called **non-metastatic castration-resistant prostate cancer (nmCRPC)**.

Today, patients with nmCRPC have three treatment options to add to ongoing treatment with standard hormone therapy: apalutamide, darolutamide, and enzalutamide. These have been shown to significantly delay progression to metastatic disease and to lengthen survival. Talk to your doctor about whether one of these drugs may be right for you. In some cases, monitoring the PSA while continuing hormone therapy may be an option for men at low risk of developing metastatic disease, particularly those with longer PSA doubling times (greater than 10 months).

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

At some point, men who have taken hormone therapy, or are currently on hormone therapy, may see their PSA levels rise, and sites of metastatic cancer are seen on conventional imaging scans. This is called **metastatic castration-resistant prostate cancer (mCRPC)**. This means that the cancer is growing despite low testosterone. Standard hormone therapy alone is not enough for these men, and they need to use additional treatments.

Fortunately, there are many options for patients even after hormone therapy no longer works. These are briefly described in the next sections. This information may seem overwhelming at first. But it represents a lot of hope: the more we learn about prostate cancer, the more ways we have to treat it.

Remember: Clinical trials are available at all stages of prostate cancer. Ask your doctor if a clinical trial might be right for you.

Make sure to talk to your doctor about all of the possibilities, as research and our understanding of prostate cancer are constantly evolving. Sometimes, understanding why a certain option is *not* best for you can help you understand your treatment plan. Additionally, specialized testing of the tumor called **biomarker testing** may provide additional guidance as to potential treatment options (e.g., PARP inhibitor medicines for tumors with mutations in *BRCA1* or *BRCA2* genes). 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.

Androgen Receptor Pathway Inhibitors

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. Insurance coverage, prior therapies, and clinical trial options can help inform the choice.

When one androgen receptor pathway inhibitor 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 response to enzalutamide, and vice versa. Researchers are actively investigating the best strategies for patients whose cancer has become resistant to abiraterone or enzalutamide. For example, a blood test for the presence of biomarkers related to the androgen receptor (e.g., AR-V7, AR mutations) can sometimes be used to indicate whether a patient is more likely to benefit from another androgen receptor pathway inhibitor vs. docetaxel chemotherapy.

See [page 33](#) for information on side effects of these medicines.

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[®]). These medicines work by killing rapidly-dividing prostate cancer cells by disrupting the protein structures required for cells to function and divide.

Many patients who are suffering from their cancer will see their symptoms (such as pain) improve after starting chemotherapy. For patients with cancer-related symptoms, quality of life is generally better for patients who receive chemotherapy as compared with no therapy.

Platinum Chemotherapy

Platinum-based chemotherapy agents such as carboplatin (Paraplatin[®]) 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 (alone or in combination with other chemotherapies) to treat patients with very advanced prostate cancer who have exhausted all other treatment options, or in patients who have certain genetic subtypes of prostate cancer (e.g., small cell prostate cancer).

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.

Chemotherapy has some serious side effects to be aware of, including low white blood cell counts that increase the risk for severe infections. If you have symptoms such as fever and/or inability to keep food/drink down, get medical attention right away. Fatigue and numbness/weakness in your toes or fingers (called neuropathy) are also common. If you experience neuropathy, talk to your doctor so you can make a plan for how to best handle further cycles. 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.



Although some patients may feel apprehensive about starting “chemo,” prostate cancer chemotherapy drugs can actually help manage pain in patients with metastatic disease.

NEUROENDOCRINE PROSTATE CANCER (NEPC)

NEPC is a highly aggressive and lethal form of advanced prostate cancer that can develop in late-stage disease. Very rarely it can occur before hormone therapy. Currently, there are no approved treatments. Medical oncologists with expertise in treating NEPC generally use platinum-based chemotherapies, often in combination. PCF is funding multiple research projects to understand how NEPC develops, predict which tumors are more likely to “become” NEPC, and develop new therapies.



FDA-approved treatments for patients with advanced prostate cancer come into the clinic after years of rigorous research and clinical trials.

Sipuleucel-T

The immune system has the remarkable ability to kill cells considered dangerous, such as infected cells or cancer cells. However, in most patients with progressive cancer, anti-cancer immune responses either never develop or are “turned off” by the cancer. Cancer vaccines can be given as a treatment to stimulate the immune system to recognize and fight cancer cells.

Sipuleucel-T (Provenge®) is a prostate cancer cellular therapy that has been approved by the FDA for patients with mCRPC. This treatment is meant for patients with minimal or no pain and is most commonly given before chemotherapy.

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 (via IV). This process is repeated every 2 weeks for a total of 3 treatments. This immunotherapy does not typically lower PSA, treat symptoms, or improve disease response rates—however, it has been shown to prolong life. There are ongoing studies to clarify exactly how this treatment works.

Sipuleucel-T can only be given in certain centers, and you should discuss with your doctor whether it is appropriate for you. Side effects are generally limited, such as flu-like symptoms occurring within a few days after the infusion.

Pembrolizumab

Pembrolizumab (Keytruda®) is a type of immunotherapy. It takes the “brakes” off of the immune system and activates tumor-killing immune cells. Pembrolizumab is FDA-approved for the treatment of all solid tumors, including prostate cancer, that have certain types or numbers of mutations (see [What is Precision Medicine? on page 39](#)).

Your doctor will order tests of your biopsies or tumor material from your prostate surgery. Studies suggest that approximately 3%–5% of patients with metastatic prostate cancer have the specific mutations in their tumor. Patients who qualify for this therapy must have progressed on prior treatment and have no satisfactory alternative treatment options.

Pembrolizumab is delivered intravenously once every 3 weeks. Because it works by modifying the immune system, there are rare but serious side effects related to overactive immune responses. These are typically treated by stopping the drug and, in some cases, starting steroids or other immune-suppressive medications.

PARP Inhibitors

PARP inhibitors are a class of precision medicines: patients are eligible for therapy if they have mutations in certain genes involved in DNA repair. These “DNA damage repair” (DDR) genes include the prostate, breast, and ovarian cancer risk genes *BRCA1* and *BRCA2*, as well as others. PARP inhibitors currently FDA-approved for mCRPC are: olaparib (Lynparza®), rucaparib (Rubraca®), talazoparib (Talzenna®; in combination with enzalutamide) and niraparib (in combination with abiraterone as Akeega®). There are some differences in the use of each drug, such as the specific gene mutations used to select patients, how they may be combined with androgen receptor pathway inhibitors, and the timing of when they can be given in the course of mCRPC. Potentially serious side effects include bone marrow problems (anemia), lung inflammation (pneumonitis), and blood clots.

A sizable proportion of patients with metastatic prostate cancer have these mutations and thus may be candidates for treatment with PARP inhibitors: Up to 25%–30% have these mutations (inherited or acquired) 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, and results in cancer cell death.

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

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.

Patients with metastatic prostate cancer should strongly consider genetic counseling and genetic testing for inherited mutations. See [Chapter 6](#) for more information.

PSMA Radionuclide Therapy

PSMA (prostate-specific membrane antigen) is a protein that is found at high levels on the surface of prostate cancer cells. PSMA radionuclide therapy is a new type of treatment consisting of radioactive molecules attached to molecules that target prostate cancer cells by seeking the PSMA protein. They are injected into your bloodstream and the radiation is brought directly to the cancer cells. As of 2025, ¹⁷⁷Lutetium-PSMA-617 (Pluvicto®) is approved for patients with mCRPC who have received an androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy (such as docetaxel) or who are considered appropriate to delay chemotherapy. Patients must have cancer visible on a PSMA PET scan ([see page 16](#)).

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. Other potentially more potent versions of PSMA radionuclide therapies are also in development. Because small amounts of PSMA are present on certain types of healthy tissues, there can be side effects. Rare, potentially serious side effects, include bone marrow problems and kidney problems, may also occur. Ask your doctor about radiation safety precautions you should take in the days following each infusion to minimize risk to you and your family.

Radium-223

Radium-223 (Xofigo®) is a radiopharmaceutical chemically similar to calcium that is used to treat CRPC in patients with painful bone metastases. Because of its calcium-like chemical properties, radium-223 is absorbed in areas where bone is actively growing and healing, in place of calcium. Treatment with radium-223 both prolongs survival and improves quality of life, prolonging time to potential complications of advanced prostate cancer (such as pain, bone fractures, or spinal cord compression). Talk with your doctor about whether you should also receive a bone health agent ([see page 38](#)) when you are starting treatment with radium-223.

External Beam Radiation Therapy (EBRT)

Radiation therapy can be used in multiple ways in patients with metastatic prostate cancer. Use of radiation therapy in patients with mHSPC is discussed on [page 32](#). In mCRPC, it is largely used for palliative purposes, that is, to alleviate symptoms due to the cancer, such as pain, nerve compression, urinary obstruction, or bleeding. 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, they can lead to bone pain, fracture, or other complications that can significantly impair a patient's health.

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 early salvage radiotherapy with or without hormone therapy ▶ Enzalutamide (with or without hormone therapy) in patients with a rapid PSA doubling time after initial treatment with surgery or radiation therapy ▶ Alternative option for patients with a slow PSA doubling time and/or limited life expectancy: surveillance or observation
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) with or without androgen receptor pathway inhibitor* or docetaxel ▶ Hormone therapy + (androgen receptor pathway inhibitor* OR docetaxel) ▶ Hormone therapy + darolutamide + docetaxel
Non-metastatic castration-resistant prostate cancer <i>Rising PSA but no detectable tumors on conventional imaging in patients who are on continuous hormone therapy</i>	<ul style="list-style-type: none"> ▶ Observation + continued hormone therapy for select patients with prolonged PSA doubling times ▶ Hormone therapy + (enzalutamide OR darolutamide OR apalutamide)
Metastatic castration-resistant prostate cancer <i>Rising PSA with tumor(s) detectable on imaging despite hormone therapy</i>	<ul style="list-style-type: none"> ▶ Abiraterone or enzalutamide ▶ Radium-223 (for treatment of symptomatic bone metastases) ▶ Docetaxel or cabazitaxel chemotherapy ▶ ¹⁷⁷Lutetium-PSMA-617 (if tumors visible on PSMA PET scan) ▶ Sipuleucel-T (if minimal symptoms) ▶ PARP inhibitors (if DNA damage repair gene alterations are present)
Patient has exhausted all therapeutic options	<ul style="list-style-type: none"> ▶ Platinum chemotherapy ▶ Pembrolizumab (if cancer has certain types or numbers of mutations)
Bone protective agents	<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.

Decades ago, patients had few treatment options. Today, there are more than 25 FDA-approved medicines for prostate cancer.

Treatment with medicines called bisphosphonates (zoledronic acid; Zometa®) or denosumab (Xgeva®) can help prevent complications related to bone metastases. Risks with these drugs include osteonecrosis of the jaw, which is rare, but can result in jaw pain and poor healing of your teeth. Your doctor will monitor certain lab values regularly. Typically, your doctor will also recommend a thorough dental exam prior to starting these agents. Discuss the need for calcium and vitamin D supplements with your doctor.

CLINICAL TRIALS AND FUTURE DIRECTIONS

What is Precision Medicine?

Precision medicine uses new tests to target treatment, based on the unique features of a patient's cancer. Think of it like taking your cancer's fingerprint. Because every cancer fingerprint can be different, each cancer needs a custom treatment. We don't yet have treatments tailored for every patient's prostate cancer, but we can test tumor DNA (in tumor tissue and circulating in the blood) and inherited DNA (in blood or saliva) to see if certain therapies (such as PARP inhibitors or immunotherapy) may be effective. Ask your doctor about **biomarker testing** and **genetic testing for inherited mutations** (see box) to see if there is a specific treatment for your type of cancer. Your doctor can help you make an informed decision about the options.



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.

CANCER TESTING TERMINOLOGY

The terms used for the many different types of testing can be confusing. **Biomarker testing** looks at tumor tissue for characteristics that may be used to help select your treatment. In some situations, a blood sample will be tested. These characteristics may have been present when the tumor started or may be acquired as the tumor grows. You may also hear this called **somatic testing**.

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 (see Chapter 6).



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.

The Future Landscape of Prostate Cancer Therapy

There are nearly 1,000 ongoing clinical trials in prostate cancer just in the U.S. that are testing new therapies and therapeutic strategies, with many more worldwide. While only a few of these will ultimately lead to new treatments or practice-changing solutions, there are several promising approaches that should be noted. Some are in small, early-phase clinical trials, while others are in large comparative trials that may lead to FDA approval in the near term. Consult your doctor to find out about joining a clinical trial or to check the status of FDA approval.

Current areas of exploration in prostate cancer treatment include:

- ▶ **Moving therapies to earlier states of prostate cancer:** Treatments currently approved for mCRPC are being tested in patients whose prostate cancer is still responsive to hormone therapy, such as PARP inhibitors and PSMA radionuclide therapy
- ▶ **New combinations:** Giving existing, approved treatments together may be synergistic and lead to better patient outcomes, such as PSMA radionuclide therapy with immunotherapy
- ▶ **New targets:** Clinical trials are being conducted to test therapies that target genes such as *PTEN*, *Wnt*, *CDK12*, *CHEK2*, *MYC*, and others
- ▶ **Therapies currently used in other cancers that may be applied to prostate cancer**
- ▶ **Novel approaches such as CAR-T cells** (“chimeric antigen receptor”)–T cells (immune cells) taken from a patient and genetically engineered to target and kill tumor cells
- ▶ **Bipolar androgen therapy (BAT):** Testosterone levels are cycled between supraphysiologic (very high) and castrate (very low) levels to re-sensitize patients to drugs such as abiraterone or enzalutamide
- ▶ **Diet and exercise:** Understanding how patients can change their health habits to lower their risk of prostate cancer progression and improve survivorship and quality of life

Clinical trials are available across all stages of prostate cancer. Start by speaking with your doctor. The website clinicaltrials.gov is a searchable master list of trials.

Clinical Trials: How to Get Involved

Finding new treatments, and how to best use existing treatments, is evaluated by clinical trials. Researchers test the hypothesis that a certain treatment may be effective for patients, under certain conditions. Clinical trials play a vital role in bringing new treatments to patients who need them most, securing data so that FDA approval can be obtained, and new drugs can be used in widespread clinical practice. There are currently more than 25 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 rigorous testing in multiple trials over several years.

Although they are often perceived as being a “last resort” for patients who have exhausted all other treatment options, in fact, trials span the prostate cancer experience, from better treatments for localized prostate cancer, to life-prolonging drugs for advanced disease, to symptom management, to changes in diet and exercise which can improve patient outcomes and survivorship.

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, in earlier-phase trials, every patient gets the new medicine, and when patients are included in phase 3 randomized trials, patients in the “control” group still receive the minimum standard of care.



“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

GET INVOLVED!

Patients who participate in clinical trials become citizen scientists, providing an invaluable service both to treatment science and fellow patients. During the course of treatment, you may have the opportunity to join an observational study that does not affect your treatment, but adds to the body of data. This can be a great way for people going through cancer to “give back” to the greater body of knowledge.

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

– PATIENT



WELLNESS IS ESSENTIAL

From the moment you are diagnosed with prostate cancer, it is important to make mindful decisions about your diet and exercise habits. Your everyday choices are vital to the success of your treatment, and are a way to take back some of the control that cancer and its treatment may have had on your life. Additionally, prostate cancer patients, like the general population, are still at high risk for cardiovascular disease and its complications; thus a healthy lifestyle is still very important after a prostate cancer diagnosis.

Scientific evidence strongly suggests that healthy habits, such as good nutrition and regular exercise, may actually slow the growth and progression of prostate cancer. While it may seem as though the latest news on specific foods and exercise regimens changes constantly, in fact, many studies converge on a few basic principles. For example, choose vegetables, whole grains, and a modest amount of healthy added fat (e.g., olive oil), while minimizing your intake of packaged “junk” foods and processed meat. To stay up to date on the latest research, subscribe to the Health and Wellness newsletter at pcf.org.

NUTRITION

Just a few simple changes in your daily eating habits can help support healthier living during treatment. These changes may speed your time to return to more normal function and may even decrease risk of your cancer getting worse. All these recommendations also apply to maintaining overall health, for you and your family. An anti-inflammatory, heart-healthy diet gives every prostate cancer survivor a better chance to maximize longevity through health practices.

1. Brightly colored vegetables. Incorporate vegetables such as 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. For example, consuming whole milk is linked to increased risk of prostate cancer progression and lethal disease. Healthy fats include avocado and olive oil. Avoid processed meats (lunch meats) that contain nitrates, and charred meat, which have been shown to have cancer-promoting properties. Emphasize plant-based proteins such as nuts and beans instead, with lean poultry or fish as additional options.

3. Whole, minimally processed foods. You want everything you eat to pack the most nutritional “punch.” Whole foods contain vitamins, nutrients, and, importantly, fiber—and are less calorically dense. For example, for breakfast, prepare a vegetable scramble with a side of berries, rather than microwaving a packaged sausage biscuit sandwich.

For more tips, see PCF’s guide, *The Science of Living Well, Beyond Cancer*.

As much as possible, choose minimally processed, nutrient-dense foods. Go for high fiber and low added sugars.



Fish, berries, cooked tomatoes, and broccoli are just some of the foods that can help support your overall health during treatment.

EXERCISE

Exercise is an essential healthy habit. More research is emerging to suggest that exercise during cancer treatment can improve long-term survival when combined with traditional therapies. It helps you to function better and tolerate your treatments. Exercise improves quality of life in patients with prostate cancer, supporting better sleep and cognition, and reduced depression and anxiety. These benefits are seen in patients with advanced prostate cancer. Although it may seem counterintuitive, regular exercise actually reduces fatigue and increases energy.

If you are living with advanced prostate cancer, check first with your doctor about what types of exercise are safe for you. Exercise is still safe, but your doctor will need to consider precautions based on any sites of metastases as well as your other medical conditions. You may be able to start with regular walking. Do not be discouraged if you cannot walk as far as you used to; start with short distances and gradually build your endurance.

Before beginning an exercise program, speak with your doctor about how to do so safely. Depending on the state of your cancer and any other health concerns, you may need close supervision.

Strength training or resistance exercises can help prevent the muscle and bone loss that happens with aging. This is particularly important for patients taking hormone therapy, in whom the process is further accelerated by removal of testosterone. Again, check with your doctor about how best to do these safely. You may be able to start with simple body-weight resistance exercises such as squats (holding on to a chair for support) and push-ups (can be done on your knees).

How does it work? Research suggests that exercise affects energy metabolism, oxidative stress, immunity, and androgen signaling pathways, and is therefore beneficial for men with prostate cancer. Exercise also reduces levels of inflammation that can contribute to prostate cancer growth. The key is consistency: exercise as regularly as you can and increase the intensity of your exercise as you are able.

OTHER HEALTH FACTORS

In addition to diet and exercise, there are important other health factors to consider.

Smoking

Quitting smoking may reduce the risk of dying from prostate cancer and reduces the risk of dying from any cause. The overall health benefits from quitting begin on the first day after smoking ceases, so it is never too late to quit. Why is this important? Smokers may have a higher risk of prostate cancer progression, as well as an increased likelihood of death from prostate cancer and overall mortality. However, research suggests that **past** smokers do **not** have an increased risk of death from prostate cancer, which highlights the benefits of smoking cessation in prostate cancer survivors. Quitting smoking is also associated with improved penile blood flow and erections; erectile dysfunction is a common side effect of prostate cancer treatments.

Quitting smoking reduces the risk of dying from any cause. If you need help to quit, speak to your doctor about options.

Mental and Emotional Health

Prostate cancer can bring with it a lot of negative emotions and experiences: fear, worry, mood changes, distress, sleeplessness, irritability, and fatigue. Research has shown that 6 in 10 men with prostate cancer experience mental health distress, with 10%–40% having significant depression. Depression itself can affect sleep, appetite, and memory. Some of the treatments for prostate cancer themselves can also have effects on mental health. For example, hormone therapy can affect mood and thinking.



Maintaining a positive attitude along with healthy diet and regular exercise will help during treatment and improve your quality of life.

If you are struggling with stress, worry, and/or mood, know that this is common, and that you are not alone. It can be hard to raise the topic with your doctor; during an office visit that is focused on managing your cancer, he or she may not proactively ask about how you are coping. Ask your doctor or oncology nurse about resources such as support groups, social workers, chaplains, therapists, and psycho-oncologists. In addition, you can try strategies on your own to manage your response to stress, such as exercise, spending time with family and friends, and meditation.

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

“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 CANCER 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. For example, you may have heard of the *BRCA1* and *BRCA2* gene mutations that increase the risk for not only breast and ovarian cancers, but also for prostate, pancreatic, gastrointestinal cancers, and others.

There are three important things you should know about prostate cancer and your family:

1. Prostate cancer is one of the most heritable cancers.

This means that of many of the major cancers out there—breast cancer, lung cancer, colorectal cancer, kidney cancer, and others—more cases of prostate cancer are a result of being passed down through the generations. (See page 5 to understand other factors that increase risk.)

2. The same genes that cause prostate cancer to be passed down through the generations can increase risk for many other cancers. This means that if you have prostate cancer in your family, your family members—men and women—are also at higher risk for other cancers, particularly breast, colon, ovarian and pancreatic. Similarly, if colon cancer runs in your family, the men in the family are also at a higher risk for prostate cancer.

3. More and more, science is discovering that health habits can play a significant role in cancer outcomes. PCF-funded research has shown that even if you are more genetically predisposed to prostate cancer, eating healthy and exercising can help decrease your risk for more aggressive disease.

More than 20 genes are linked to inherited prostate cancer. Some of these genes may overlap with other types of cancer.

For years, a diagnosis of cancer was seen as something to hide—a sign of weakness, to be kept to yourself. Stories exist of wives who didn't know their husbands had prostate cancer until after they had already had surgery for it. Needless to say, in those days, once a man was through his recovery, it was never talked about again. Now, we know more, and this is a very important point to remember:

Talking openly about your health and conditions is the key to keeping your whole family safe.

HOW GENES CAN CAUSE PROSTATE CANCER

In school, you may have learned that genes from each parent combine when a child is conceived, giving children a blend of their parents' traits and characteristics. We now know that your body contains over 20,000 genes that you inherited from your parents. Together, these genes are like instructions that tell your body how to grow and operate.

When a gene's instructions change, that is called a genetic mutation (mutation means change). Changes can happen at any stage—from immediately after conception in the womb to late in life due to environmental factors (for example, smoking), or even simply the aging process.

So far, scientists have identified over 20 genes that are linked to inherited prostate cancer. We now also know that combinations of certain gene mutations increase risk for prostate cancer. Researchers are developing a "polygenic risk score" that will someday look across many ("poly") genes to assess a person's risk of prostate cancer. Additionally, scientists are working to include minority groups, such as Black patients, in these studies to best inform all patients of their genetic risk.



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

UNDERSTANDING YOUR RISK: TAKE ACTION

If you've been diagnosed with prostate cancer, this can present an opportunity to open up a conversation with family members—both male and female—about what this may mean for their health. Based on what you and your family discover together, there are several proactive steps you can take related to cancer screening and genetic testing.

1. Have a conversation with your family

Male health issues, especially ones that may affect sexual organs, can be a taboo and unwelcome conversation. Men who are still sexually active may fear the potential of being perceived as “less of a man;” others may be shy to speak with their sons

and daughters. While this is understandable, it is not a good approach. It is important to speak with family and friends about the importance of early detection for prostate cancer. This disease should not be swept under the rug: the later it is found, the harder it is to treat. By starting a conversation about cancer, you could be saving a life—possibly even your own or someone in your family.

2. If recommended by your doctor, seek genetic counseling

Genetic counselors specialize in the inherited risk of cancer in families. If this guide has alerted you to the fact that your genetic profile may mean you are at a higher risk of developing cancer, the first place to start is with your primary care physician. Talk to your doctor about a referral to a genetic counselor if you have 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
- ▶ Ashkenazi Jewish ancestry

Your Family

- ▶ One or more close blood relatives with prostate cancer diagnosed at age younger than 60, or with metastatic prostate cancer at any age, or who died of prostate cancer
- ▶ 2 or more close blood relatives on the same side of the family with any of the following cancers: breast, colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma (tell your doctor about all cancers in the family)
- ▶ Blood relative with a known cancer risk gene mutation (e.g., *BRCA1*, *BRCA2*, Lynch syndrome)

3. Get tested

“Cascade genetic testing” is a specialized form of screening that identifies whether family members share a genetic mutation. For example, if a man discovers that he is a carrier of inherited genes that increases the risk for prostate cancer, this has critical implications for all his family members, who may have inherited the same mutation. 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.

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. 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.

The National Society for Genetic Counselors has a list of members at nsgc.org. There are also telehealth genetic counseling services available. If you do not have medical insurance, ask your doctor about research studies you may be eligible for. Testing may be paid for by the study.

Note that recreational tests (such as 23andme) are not FDA-approved for health-related screening use and should not be considered an adequate substitute for comprehensive genetic testing for inherited cancer risk mutations.

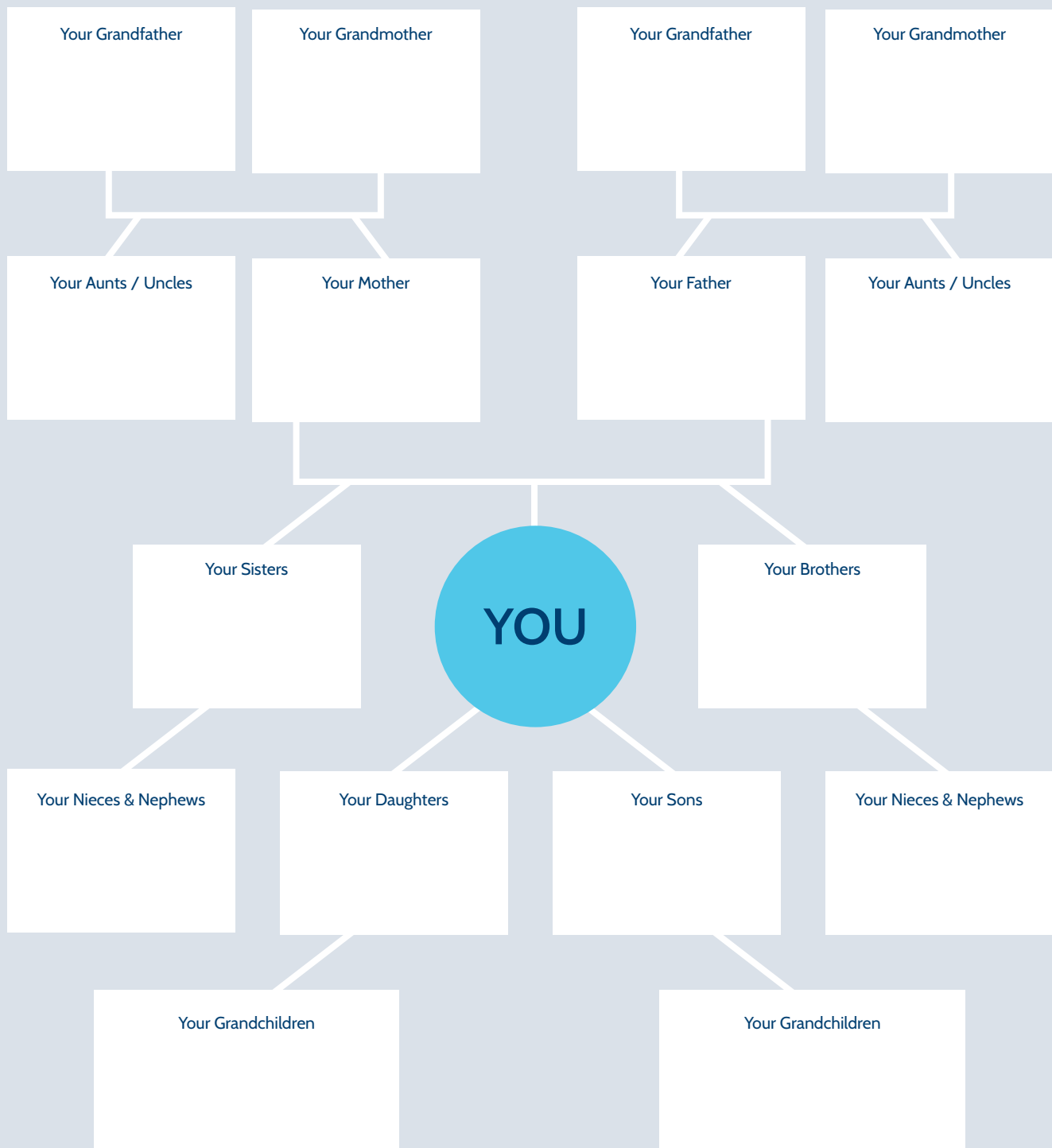


Learning more about your genetic profile today may make a difference in the lives of your children and grandchildren as they grow and age.

4. Have another conversation with your family

One conversation—the one where you tell everyone you have prostate cancer—is not enough. As more information becomes available, either because of additional test results or because of new circumstances, such as another diagnosis in the family, it is important to update everyone. You can use the Family Tree tool on the next page to keep track. This is most important for your sons and daughters. Why? Because cancers that run in families are often the most aggressive types of cancer. Your adult children may need to consider screening at an earlier age to have a greater chance of catching cancer earlier.

TOOL: CANCER FAMILY TREE



Individuals who have a family history of prostate, breast, colon, ovarian, pancreatic, or multiple other cancers should discuss screening with their doctors. They may need to be screened earlier and/or more frequently.

Production generously supported by



Supporters of this guide were not responsible for nor consulted on the development of the content contained inside.

Prostate
Cancer
Foundation

www.pcf.org

1250 Fourth Street, Santa Monica, CA 90401 | 800.757.CURE (2873)

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