Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Prostate Cancer

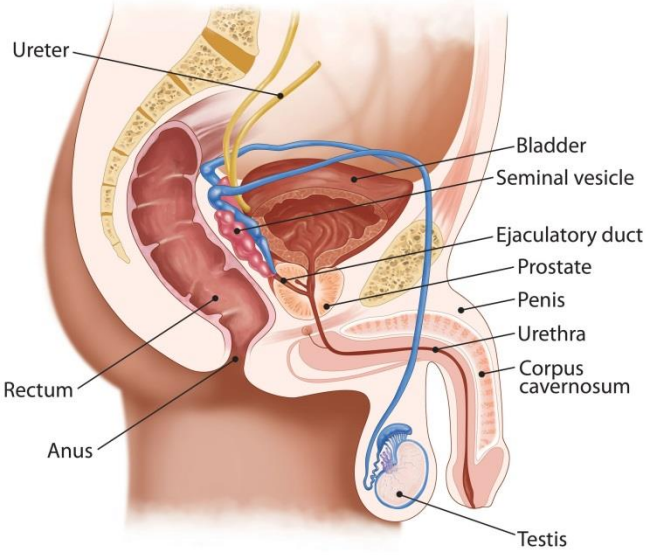
Introduction

The prostate gland is part of a man's reproductive and urinary systems. The prostate is oval shaped with a rounded tip. It is approximately 4 cm wide and 3 cm thick. The actual size of the prostate varies from man to man. It can range from the size of a walnut to that of a golf ball.

Review of Anatomy and Physiology

The prostate surrounds the base (or neck) of the bladder. It has 2 lobes that surround the urethra. The urethra carries urine from the bladder, through the prostate, and out through the tip of the penis.

The prostate gland is covered in a layer of connective tissue called the prostatic capsule.



[Picture Credit: Prostate Gland]

The prostate contains two main types of tissue: exocrine glandular tissue and fibromuscular tissue.

- Exocrine glandular tissue in the prostate is epithelial tissue specialised for the secretion of the components of semen. Most of the prostate is made of exocrine glandular tissue, as the prostate's primary function is the production of semen.
- Fibromuscular tissue is a mixture of smooth muscle tissue and dense irregular connective tissue containing many collagen fibres. The collagen fibres of the tissue provide strength to the tissue while the smooth muscle permits the tissue to contract to expel fluids. Fibromuscular tissue forms the outermost layer of the prostate and the tissue surrounding the urethra.

Some structures around the prostate are:

- seminal vesicles – These glands produce semen and are found on both sides of the prostate.

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- vas deferens – These tubes carry sperm from the testicles to the seminal vesicles.
- nerve bundles – These nerves control bladder and erectile function and are found on both sides of the prostate.
- muscles – These muscles control urination.

The prostate gland is divided into 3 zones:

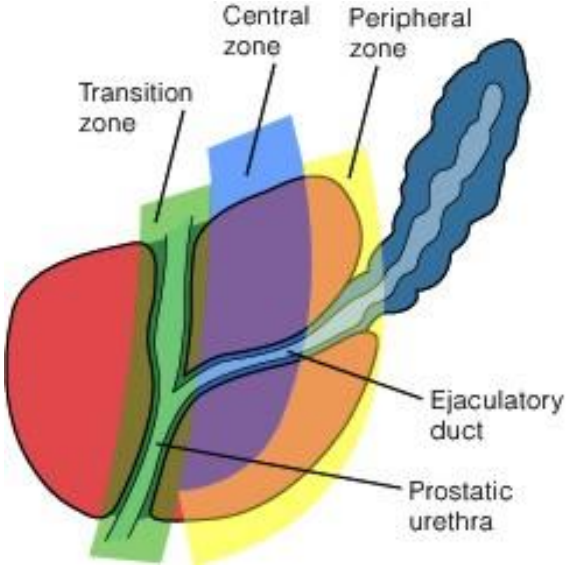
- peripheral zone
- transition zone
- central zone

Peripheral zone - the peripheral zone is the area of the prostate that is closest to the rectum. It can easily be felt during a digital rectal examination (DRE). It is the largest zone of the prostate gland.

The majority of prostate tumours (approximately 75%) are found in the peripheral zone.

Transition zone - the transition zone is the middle area of the prostate, between the peripheral and central zones. It surrounds the urethra as it passes through the prostate. This zone makes up about 20% of the prostate gland until the age of 40.

As men age, the transition zone begins to enlarge, until it becomes the largest area of the prostate. This is called benign prostatic hyperplasia (BPH). When the transition zone enlarges, it pushes the peripheral zone of the prostate toward the rectum.



[Picture Credit: Prostate Gland Zones]

Central zone - the central zone is in front of the transition zone. It is the part of the prostate that is farthest from the rectum. Because of this, prostate tumours in this zone cannot be felt by the doctor during a DRE.

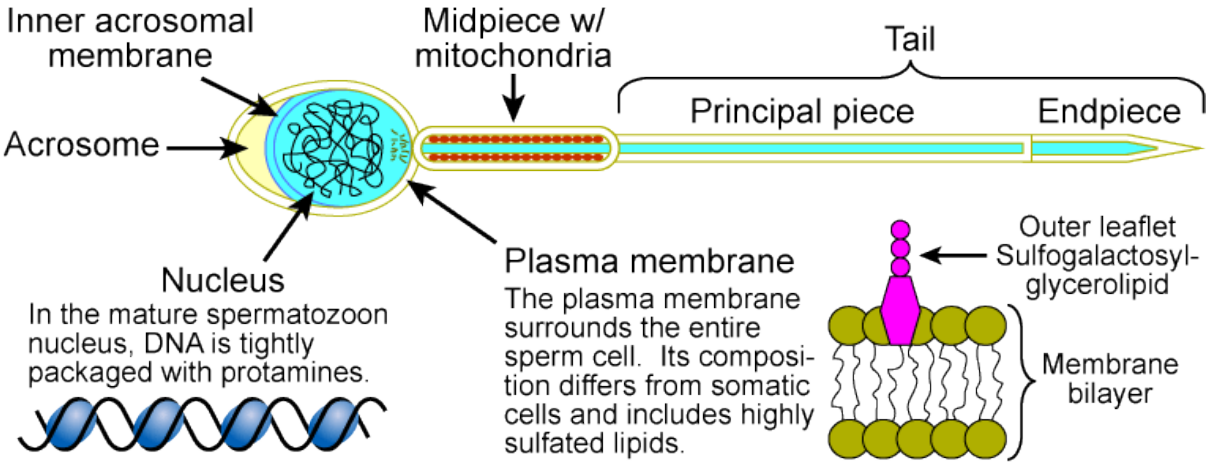
The main function of the prostate gland is to produce the fluid portion of semen. The gland cells within the prostate produce a thin fluid rich in proteins and minerals that maintain and nourish sperm. This fluid is made continuously. The excess fluid passes from the body in the urine. When a man is sexually aroused, the prostate produces larger amounts of this fluid. It then mixes with sperm and is ejaculated as semen.

The prostate gland also plays a part in controlling the flow of urine. The urethra runs from the bladder, through the prostate, and out through the penis. The muscle fibres of the prostate are wrapped around the urethra and are under involuntary nervous system control. These fibres contract to slow and stop the flow of urine.

Semen

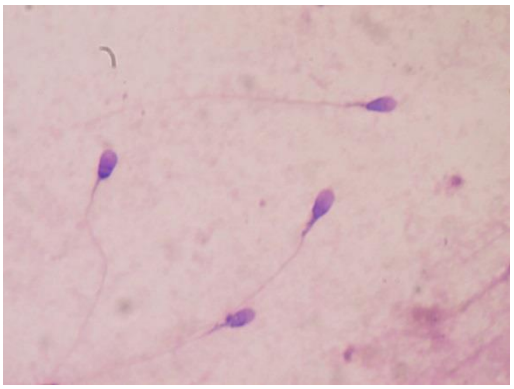
Semen is a fluid of complex composition, produced by the male sex organs. There is a cellular component, spermatozoa, and a fluid component, seminal plasma. An average

ejaculate is 3 to 4 ml containing 70 to 150 million sperm. Sperm are the male reproductive cells. Each consists of a head, tail and mid-piece. In humans, the head is a tiny disc, about 4.5 µm long and 2.5 µm wide. The tail is about 40 µm long, and is rapidly lost after ejaculation. The head is where the DNA is preserved. The sperm of apes are similar in size and shape as that of humans. Dogs have similarly shaped sperm but about one third the size of human sperm. Other animals have differently shaped sperm.



[Picture Credit: Sperm]

In the human male, sperm cells are produced by the testes (singular, testis); they constitute only about 2 to 5 percent of the total semen volume. During the process of ejaculation, liquids from the prostate gland and seminal vesicles are added, which help dilute the concentration of sperm and provide a suitable environment for them. Fluids contributed by the seminal vesicles are approximately 60 percent of the total semen volume; these fluids contain fructose, amino acids, citric acid, phosphorus, potassium, and hormones known as prostaglandins. The prostate gland contributes about 30 percent of the seminal fluid; the constituents of its secretions are mainly citric acid, acid phosphatase, calcium, sodium, zinc, potassium, protein-splitting enzymes, and fibrolysin (an enzyme that reduces blood and tissue fibres). A small amount of fluid is secreted by the bulbourethral and urethral glands - this is a thick, clear, lubricating protein commonly known as mucus. The prostate is the source of the enzyme acid phosphatase and the protein Prostate Specific Antigen, or p30 protein.



[Picture Credit: Stained Sperm Cells]

After ejaculation, during intercourse, semen is lost by drainage and by biochemical change. (Inner Body; Canadian Cancer Society; James Buchanan Brady Urological Institute; National Forensic Science Technical Center; Encyclopaedia Britannica).

Cancer of the Prostate Gland
Cancer begins when normal cells in the prostate change and grow uncontrollably, forming a mass called a tumour. A tumour can be benign or malignant.

Prostate cancer is a malignant tumour that begins in the prostate gland. Some prostate cancers grow very slowly and may not cause symptoms or problems for years. However, most prostate cancer cells make excessive amounts of a protein called prostate specific antigen (PSA). PSA is also found in higher-than-normal levels in men with various other prostate conditions, such as benign prostatic hyperplasia (BPH) and prostatitis, in addition to prostate cancer.

Prostate cancer is somewhat unusual, compared with other types of cancer, because many tumours do not spread from the prostate. And often, even metastatic prostate cancer can be successfully treated, allowing men with prostate cancer to live a good health for several years. However, if the cancer does metastasise to other parts of the body and cannot be well controlled with treatment, it can cause pain, fatigue, and other symptoms.

Often, when a man develops prostate cancer later in life, it is unlikely to cause symptoms or shorten the man's life, and aggressive treatment may not be needed. For this reason, early detection for prostate cancer with prostate specific antigen (PSA) testing in men who do not have symptoms of the disease is controversial.
(Cancer.Net).

Differential Diagnosis
The following table provides an overview of the signs and symptoms of prostate problems. Individuals with any of the symptoms listed below should contact a medical professional:

Symptom	Acute Prostatitis	Chronic Prostatitis	Benign Enlarged Prostate	Prostate Cancer
Pain or burning sensation when urinating (dysuria)	x	x	x	
Difficulty urinating, such as dribbling or hesitant urination	x	x	x	x
Frequent urination, particularly at night (nocturia)	x	x	x	x
Urgent need to urinate	x	x	x	x
A urinary stream that starts and stops	x	x	x	x
Pain in abdomen, groin or lower back	x	x		x
Pain or discomfort of the penis or testicles	x	x		x
Pain in the area between the scrotum and rectum (perineum)	x			
Pain in abdomen, groin or lower back	x	x		x
Painful orgasms (ejaculation)	x	x		x
Flulike symptoms (with bacterial prostatitis)	x	x		
Feels like bladder does not empty completely		x	x	
Erectile dysfunction	x	x	x	x
Decreased urinary stream	x	x	x	x
Blood in semen	x	x		x
Blood in urine	x	x	x	x
Raised Prostate Specific Antigen (PSA)	x	x	x	x
Bone pain				x

(WebMD; Prostate Cancer UK; Mayo Clinic; Urology Care Foundation; American Cancer Society; Healthline; Mescape).

Incidence of Prostate Cancer in South Africa

According to the National Cancer Registry (2012) the following number of prostate cancer cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	No of Cases	Lifetime Risk	Percentage of All Cancers
All males	6 807	1:19	18.45%
Asian males	155	1:32	18.45%
Black males	2 763	1:30	23.68%
Coloured males	875	1:12	20.17%
White males	3 014	1:11	15.03%

The frequency of histologically diagnosed cases of prostate cancer in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	3	3	6	103	1 023	2 454	2 237	878
Asian males	0	0	0	2	13	56	50	24
Black males	1	2	3	50	422	959	796	328
Coloured males	1	1	0	15	152	296	277	88
White males	1	0	1	33	390	1 042	1 002	389

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Types of Prostate Cancer

By the age of about 50, about half of all men have small changes in the size and shape of the cells in the prostate. This is called prostatic intraepithelial neoplasia (PIN). Some research has indicated these cellular changes may eventually develop into prostate cancer. This is controversial and preventive treatment is not recommended.

If PIN is present, the best strategy is to be certain a thorough biopsy procedure shows not invasive cancer. If PIN is the only finding, then careful follow-up screening with a PSA blood test and digital rectal examination is recommended.

More than 9 out of 10 prostate cancers (90%) are a type called acinar adenocarcinoma. It starts from gland cells in the prostate. Many of these cancers grow extremely slowly and are not likely to spread. But some can grow more quickly. There are other types of adenocarcinoma, which include atrophic, foamy, colloid and signet ring carcinoma. They are all treated in the same way as acinar adenocarcinoma.

The remaining 1 in 10 prostate cancers include the following types:

- Ductal adenocarcinoma
- Transitional cell (or urothelial) cancer
- Squamous cell cancer
- Carcinoid
- Small cell cancer
- Sarcomas and sarcomatoid cancer

Because these cancers are so rare, there is sometimes very little information about which treatments work best.

Ductal adenocarcinoma - this type of prostate cancer starts in the cells that line the ducts of the prostate gland. It tends to grow and spread more quickly than acinar adenocarcinoma. This is why some men have an advanced prostate cancer when they are diagnosed. This type of cancer is less sensitive to hormone therapy than acinar adencarcinoma.

Transitional cell (urothelial cancer) - this type of prostate cancer also starts in the cells that line the urethra. More commonly, this type of cancer may start in the bladder and spread into the prostate. Transitional cell cancer of the prostate may spread into the bladder entrance and into nearby tissues.

Squamous cell cancer - squamous cell prostate cancer starts from the squamous cells covering the prostate gland. Squamous cell prostate cancer tends to grow and spread more quickly than adenocarcinoma of the prostate. This is why some men have an advanced prostate cancer when they are diagnosed.

Carcinoid of the prostate - carcinoid tumours start from cells of the neuroendocrine system, which is made up of specialised nerve and gland cells.

These tumours are very rare and seem to be slow growing, although some of them may be more aggressive. They may not cause any symptoms for many years.

Small cell cancer - this is a type of neuroendocrine tumour and is made up of small round cells. This type of cancer often cause a raised prostate specific antigen (PSA) test. Many men are diagnosed when it is already advanced. Small cell prostate cancer tends to grow and spread more quickly than adenocarcinoma of the prostate. Hormone therapy does not work for this type of prostate cancer.

Sarcoma and sarcomatoid cancer - sarcomas start from muscle cells. They often grow quite quickly. The most common type of prostate sarcoma in adult men is leiomyosarcoma. It tends to occur in men between the ages of 35 and 60.

Sarcomatoid cancers have a mixture of sarcoma and adenocarcinoma cells.
(Cancer Research UK; MD Anderson Cancer Center).

Risk Factors for Prostate Cancer

Age is the strongest risk factor for prostate cancer. Prostate cancer is very rare before the age of 40, but the chance of having prostate cancer rises rapidly after age 50.

Other possible risk factors include:

- Family history: Prostate cancer seems to run in some families, and scientists have found several inherited genes that seem to raise prostate cancer risk

Risk Group	Relative Risk for Prostate Cancer (95% Confidence Index) *
Brother(s) with prostate cancer diagnosed at any age	3.14 (2.37 – 4.15)
Father with prostate cancer diagnosed at any age	2.35 (2.02 – 2.72)
One affected first-degree relative diagnosed at any age	2.48 (2.25 – 2.74)
Affected first-degree relatives diagnosed <65 years	2.87 (2.21 – 3.74)
Affected first-degree relatives diagnosed ≥65 years	1.92 (1.49 – 2.47)
Second-degree relatives diagnose at any age	2.52 (0.99 – 6.46)
Two or more affected first-degree relatives diagnosed at any age	4.39 (2.61 – 7.39)

(*) Adapted from Kiciński, at al (2011)

  If there is a family history of the BRCA1 or BRCA2 gene mutation or a very strong history of women with breast cancer, the risk for prostate cancer may be higher

- Race/ethnicity: Prostate cancer occurs more often in African-American men than in men of other races. There is no current evidence that shows that this is applicable to South African black men. In black men, prostate cancer is also said to be more aggressive or advanced. It is not clear why this is so – there is also no evidence to indicate that this applies to South African black men

- Nationality: Prostate cancer is most common in North America, north western Europe, Australia, Africa and Caribbean island and less common in Asia, Central America, and South America

- Diet: Men who eat a lot of red meat or high-fat dairy products appear to have a slightly higher chance of getting prostate cancer

- Obesity: Obese men diagnosed with prostate cancer may be more likely to have advanced disease that is more difficult to treat

- Use of Anabolic Steroids:- The use of anabolic steroids may have the following side effects:
-
    - Infertility (low sperm count)
    - Impotence
    - Testicular shrinkage
    - Baldness
    - Testicular/prostate cancer
    - Enlarged breast tissue

- High alcohol intake – Alcohol was declared a Group 1 carcinogen by the Interantional Agency for Research on Cancer (IARC) in 1980.

(UC Davis Comprehensive Cancer Center; Mayo Clinic; University of Northern Colorado; MedlinePlus).

Signs and Symptoms of Prostate Cancer
Signs and symptoms of prostate cancer can be divided as follows:

Urinary symptoms of prostate cancer - because of the proximity of the prostate gland in relation to the bladder and urethra, prostate cancer may be accompanied by a variety of urinary symptoms. Depending on the size and location, a tumour may press on and constrict the urethra, inhibiting the flow of urine. Some prostate cancer signs related to urination include:

- Stranguria - a slow and painful discharge of urine, drop by drop, produced by spasmodic muscular contraction of the urethra and bladder
- Dysuria
- Pollakiuria - abnormally frequent urination
- Haematuria
- Trouble starting and stopping while urinating
- Nocturia - frequent urges to urinate at night
- Loss of bladder control
- Decreased flow or velocity of urine stream

Other prostate cancer signs & symptoms - prostate cancer may metastasise to nearby tissues or bones. Other prostate cancer symptoms include:

- Blood in semen
- Erectile dysfunction
- Painful ejaculation
- Swelling in legs or pelvic area
- Numbness or pain in the hips, legs or feet
- Bone pain that does not go away, or leads to fractures

(Cancer Research UK; Cancer Treatment Centers of America).

Differential Diagnoses
Radiologic findings of bony metastases can mimic Paget Disease of the bone. Although bony metastases are blastic in nature, lytic lesions can occur, resulting in pathologic fractures. In men treated with luteinizing hormone-releasing hormone (LHRH), osteoporotic fractures must be distinguished from pathologic fractures.

Neurologic manifestations should be underscored. Sudden onset of weakness of the legs in an elderly man with a history of prostate cancer should raise the suspicion of spinal cord compression, necessitating emergency treatment (spinal cord decompression). Although brain metastases with associated neurologic manifestations are rare, they do occur with enough frequency to deserve recognition.

Lymphomas can manifest as pelvic masses and bone lesions. Although coexistence of lymphomas with prostate cancer has been reported, it is extremely rare.

Transitional cell carcinoma and sarcoma of the prostate are more common in men who have undergone prior pelvic radiation therapy for prostate cancer than in men who have not. Likewise, squamous cell carcinoma of the prostate may be observed in men treated with

hormone therapy. All of these can present as a large pelvic mass with or without metastases.

- Acute Bacterial Prostatitis - Acute prostatitis is caused by a bacterial infection of the prostate gland. Symptoms include pain, mainly at the base of the penis and around the anus. A bladder infection commonly occurs at the same time.

- Prostatic Abscess - A prostatic abscesses can be a rare complication of prostatitis. It has become relatively uncommon in clinical practice due to antibiotic therapy in those with prostatitis. It tends to affect diabetic and immunosuppressed patients.

- Bacterial Prostatitis - Chronic bacterial prostatitis (CBP) represents a bacterial infection of the prostate gland. CBP causes an associated symptom complex, the hallmark of which is the occurrence of relapsing urinary tract infections, usually involving the same pathogen. CBP is often confused with non-bacterial prostatitis, chronic pelvic pain syndrome (CPPS), and prostatodynia (a type of inflammation of the prostate not due to bacterial infection and in which there are no objective findings, such as the presence of infection-fighting cells, in the urine of men who suffer from the disease).

  By definition, this condition is characterised by bacterial growth in culture of the expressed prostatic fluid, semen, or post-massage urine specimen. The expressed prostatic secretion (EPS) usually contains more than 10 white blood cells (WBCs) per high-power field (HPF) and macrophages (see the image below). (See Workup.)

- Benign Prostatic Hypertrophy -Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. Chronic bladder outlet obstruction (BOO) secondary to BPH may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross haematuria, and bladder calculi.

- Non-bacterial Prostatitis - Nonbacterial prostatitis refers to a condition that affects patients who present with symptoms of prostatitis without a positive result on culture of urine or expressed prostate secretions (EPS).

- Tuberculous Prostatitis - *Mycobacterium tuberculosis* bacilli are inhaled through the lungs to the alveoli, where they are phagocytosed by polymorphonuclear leukocytes and macrophages. Although most bacilli are initially contained, some are carried to the region's lymph nodes. Eventually, the thoracic duct may deliver mycobacteria to the venous blood; this may result in seeding of different organs. In addition, multiple granuloma form at the site of metastatic foci. It cannot be overemphasised that a tuberculosis expert doctor should always be involved in the care of these patients to avoid acquired resistance, which may become extremely costly and difficult to treat.

(e-medicine; Patient.co.uk; radiopaedia.org).

Diagnosis of Prostate Cancer

Caught in its early stages whilst still confined to the prostate gland prostate cancer can be cured. Testing through a Prostate Specific Antigen (PSA) blood test and Digital Rectal Examination (DRE) and subsequent prostate biopsy is currently the best available way to detect the presence of cancer.

Early detection is the key to enabling better outcomes and potential cure of prostate cancer. Accordingly, it is recommended that men over age 50, or 40 with a family history of prostate cancer, should talk to a doctor about testing for prostate cancer using the PSA test and DRE as part of their annual health check-up. Men should make an individual informed decision about testing based on the latest available evidence on the benefits and potential harms of testing and subsequent treatment for prostate cancer.

It can be life threatening to wait for symptoms to appear before seeking assessment.

Most men seek testing for prostate cancer for the following reasons:

- As part of a general check-up - usually after 50 years of age
- Due to a recent experience with a relative or friend who has suffered from prostate cancer
- A family history of prostate cancer
- A recent onset of urinary symptoms

Some men, when enquiring about prostate cancer, may be confused by conflicting views expressed about methods of diagnosing and treating the disease. Perhaps the most controversial is the view that it would be better for men not to know whether they have the disease and therefore they should not be tested or be treated.

The Prostate Specific Antigen (PSA) Test

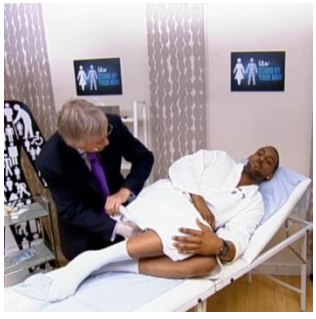
The PSA blood test looks for the presence in the blood of a protein that is produced specifically by prostate cells called Prostate Specific Antigen (PSA). The presence of an elevated PSA does not necessarily mean prostate cancer is present as there are other medical conditions that can lead to a PSA result outside the normal range.

The result of a PSA test needs expert evaluation by an experienced doctor. As a general rule, the higher the PSA result the greater the chance that prostate cancer is present. Where cancer is present, the PSA can predict the volume of disease. Where the PSA is less than 10, the cancer is commonly confined to the prostate. If the PSA is above 30, it is very likely the cancer has spread beyond the prostate and is, therefore, less likely to be curable.

If the test reveals a slightly elevated PSA, a doctor should recommend the test be repeated from time to time to establish the rate of change, if any, before recommending a biopsy.

The Digital Rectal Examination (DRE)

The DRE involves the insertion a gloved finger in the anus, where it is possible to feel part of the surface of the prostate. Irregularities include swelling or hardening of the prostate, or lumps on the surface that may indicate development of a tumour, or other problems. The drawback to this test is that one can feel only part of the prostate, so may miss irregularities beyond reach.



[Picture Credit: DRE]

Biopsy

A Biopsy is a small tissue sample taken with a spring loaded needle. This is normally conducted by a urologist. A small probe containing an ultrasound generator and sampling

needles (known as Trans Rectal Ultra Sound or TRUS) is inserted in the anus. The ultrasound generates an image of the prostate on a computer screen and guides the doctor to insert the sampling needles into selected areas of the prostate. The biopsy samples are analysed by a pathologist to determine the stage and grade of the cancer.

There are four likely results of a prostatic biopsy:

- The tissue is normal benign prostate tissue
- A condition called atypia or dysplasia where the cells do not look typical of either normal or cancerous cells
- Prostatic intraepithelial neoplasia (PIN) where the cells appear to be in the transitional stage between normal and cancer
- Prostate cancer - which are currently graded on a numerical scoring system call the Gleason Score and the Stage of cancer

(Prostate Cancer Foundation of Australia).

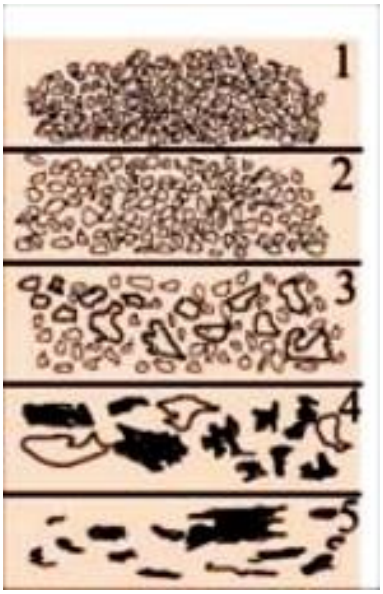
The Gleason Score

The Gleason score is used to help determine how quickly a tumour may grow or spread. It may seem confusing because with the Gleason system (the most common system used), there's both a 'grade' and a 'score'.

The Gleason grade uses numbers 1 to 5. A number is assigned to two of the areas of the prostate that have the most cancer (based on biopsy core samples that are taken). This is because the cancer may look different in each of those two areas. Once those two numbers are determined, they are added together to come up with the Gleason score, which ranges from 2 to 10.

What the Gleason grades mean

[Picture Credit: Gleason Score]



Grade 1: The cells look almost like normal cells (called *well differentiated*) and are uniformly spaced in a tight mass.

Grade 2: The cancer cells are still well differentiated, but are arranged more loosely, are more irregular in shape, and some cells have spread to other prostatic tissue.

Grade 3: The cancer is moderately differentiated; cells vary in size from small to large; and more cells have invaded other prostatic tissue.

Grade 4: The cancer cells are irregular, distorted, and look less like normal cells (called *poorly differentiated*), and there is considerable spread (called *invasion*) to other prostatic tissue.

Grade 5: The cancer cells do not look anything like normal cells and have spread in haphazard 'clumps' of all different shapes and sizes through the prostate.

What the Gleason scores mean:

- If the score is less than 6, the cancer may be considered to be well-differentiated or low-grade cancer
- A score of 7 may be considered to be moderately differentiated or intermediate-grade cancer
- A score of 8 to 10 may be considered to be poorly differentiated or high-grade cancer

According to the American Urological Association, the lowest Gleason score that is usually found after a biopsy is 5. The cancer is considered to be more aggressive as the score rises. Scores of 8 to 10 are considered to be the most aggressive, which means that the cancer is more likely to grow and spread more quickly.

The biopsy results (called the *pathology report)* will contain other important information that helps to assess how aggressive the cancer may be.

This includes:

- How many biopsy core samples were positive for cancer
- How much cancer was in each core sample (this is given as a percentage)
- Whether cancer was found in just one side of the prostate gland or in both sides (which is referred to as *bilateral)*

(Hisprostatecancer).

The Prostate Health Index (PHI) Test

Prostate Health Index (phi), a more precise blood test, outperformed traditional PSA screening in predicting clinically significant prostate cancer. There is no clear indication when this test will be available in South Africa.

The Prostate Health Index (phi), a blood test used to evaluate the probability of prostate cancer diagnosis, outperformed commonly used prostate-specific antigen (PSA) and free/total prostate-specific antigen (%fPSA) tests in predicting the presence of clinically significant prostate cancer and in improving prostate cancer detection, according to a new study.

The phi combines measurements of %fPSA (percent of protein-attached and protein-free PSA circulating in the bloodstream) and a subcategory of free PSA called pro-PSA, and is estimated to be 2.5 times more specific in detecting prostate cancer in patients than a PSA screening. The phi was approved by the US Food and Drug Administration (FDA) in June 2012 and has been available since late 2012. The study also found using a specific phi benchmark level may help identify biopsy candidates and reduce over-detection of indolent (slow-growing) prostate cancer.

“The phi can play a valuable role in determining whether an elevated PSA is likely due to prostate cancer or benign changes,” said Brant Thrasher, MD, chair of Urology, University of Kansas Medical Center, Kansas City, KS. “This option may prevent patients from potentially undergoing unnecessary biopsies.”

Study Details - Researchers at several leading institutions in the United States and the Netherlands, including Harvard Medical School and Johns Hopkins University, investigated

whether the use of phi, as compared to total PSA and %fPSA, can reduce unnecessary biopsy and over-detection of indolent prostate cancer, while improving the detection of aggressive prostate cancer.

The study consisted of 658 participants who were 50 years of age or older with a biopsy-confirmed prostate cancer diagnosis, a final PSA between 4-10 ng/mL and a benign rectal examination. Study investigators evaluated prediction of clinically significant cancer (aggressive histopathology per Epstein criteria or Gleason 7+) based on pre-biopsy measures of pro-PSA, total PSA, fPSA, %fPSA and phi and evaluated prospects for eliminating unnecessary biopsies based on results of phi prior to biopsy.

The researchers found:

- At 90 percent sensitivity, the specificity of phi was 31.1 percent, compared to 19.8 percent for %fPSA ($p=0.024$) and 10.8 percent for PSA ($p<0.001$).
- At a moderate to high phi range of 27 to 55, the probability of cancer varied from 9.8 to 50.1 percent and the probability of clinically significant cancer extended from 3.9 to 28.9 percent.
- At a phi level of 27, which is the 90 percent sensitivity cut-point, 18.8 percent of men could have been spared from undergoing prostate biopsy or over-diagnosis of non-aggressive disease.

Study investigators concluded phi outperformed PSA and %fPSA in predicting the presence of clinically significant prostate cancer and for improving prostate cancer detection. Additionally, using a phi level of 27 for selecting men for prostate cancer biopsy, when total PSA is 4 to 10 ng/mL, can decrease unnecessary biopsies and reduce over-detection of indolent prostate cancer.
(American Urological Association).

The 4Kscore Test

The 4Kscore Test combines four prostate-specific kallikrein assay results with clinical information in an algorithm that calculates the individual patient's percent risk for aggressive prostate cancer. It is said to be the only test to assess a patient's risk for aggressive prostate cancer prior to a prostate biopsy, with a 94% rate of accuracy in detecting aggressive cancer.

With the 4Kscore Test, Urologists can more confidently choose to place a low-risk patient under active monitoring or perform a biopsy on a high-risk patient based on their clinical evaluation, enhanced by the 4Kscore Test result.

The 4Kscore Test has undergone extensive clinical development and confirmation. The biomarkers utilised in the 4Kscore Test are based on over a decade of research conducted by scientists at the Memorial Sloan Kettering Cancer Center and leading research centres in Europe, encompassing over 20 000 men in Europe and the United States. The results have recently been replicated in a prospective, blinded clinical study conducted at 26 urology centres across the United States on 1 012 patients.

The test has been shown to identify the actual risk of aggressive prostate cancer for the individual patient, including high grade prostate cancer pathology and poor prostate cancer clinical outcomes within 20 years, with both high sensitivity and negative predictive value for aggressive prostate cancer.

The 4Kscore Test is not yet available in South Africa.
(OPKO Lab).

The STHLM3 Study

The Stockholm STHLM3 study was a prospective, population-based, paired, screen-positive, diagnostic study of men without prostate cancer aged 50-69 years randomly invited by date of birth from the Swedish Population Register kept by the Swedish Tax Agency. Men with prostate cancer at enrolment were excluded from the study. The predefined STHLM3 model (a combination of plasma protein biomarkers [PSA, free PSA, intact PSA, hK2, MSMB, MIC1], genetic polymorphisms [232 SNPs], and clinical variables [age, family, history, previous prostate biopsy, prostate exam]), and PSA concentration were both tested in all participants enrolled.

The primary aim was to increase the specificity compared with PSA without decreasing the sensitivity to diagnose high-risk prostate cancer. The primary outcomes were number of detected high-risk cancers (sensitivity) and the number of performed prostate biopsies (specificity). The STHLM3 training cohort was used to train the STHLM3 model, which was prospectively tested in the STHLM3 validation cohort. Logistic regression was used to test for associations between biomarkers and clinical variables and prostate cancer with a Gleason score of at least 7.

The STHLM3 model performed significantly better than PSA alone for detection of cancers with a Gleason score of at least 7 ($p<0{\cdot}0001$), the area under the curve was 0·56 (95% CI 0·55-0·60) with PSA alone and 0·74 (95% CI 0·72-0·75) with the STHLM3 model. All variables used in the STHLM3 model were significantly associated with prostate cancers with a Gleason score of at least 7 ($p<0{\cdot}05$) in a multiple logistic regression model. At the same level of sensitivity as the PSA test using a cutoff of ≥3 ng/mL to diagnose high risk prostate cancer, use of the STHLM3 model could reduce the number of biopsies by 32% (95% CI 24-39) and could avoid 44% (35-54) of benign biopsies.

The STHLM3 model could reduce unnecessary biopsies without compromising the ability to diagnose prostate cancer with a Gleason score of at least 7, and could be a step towards personalised risk-based prostate cancer diagnostic programmes.
(Grönberg, *et al.,* 2015).

Staging of Prostate Cancer

Like other forms of cancer, the prognosis for prostate cancer depends on how far the cancer has spread at the time it is diagnosed. A system of staging is used to describe prostate cancer spread. Accurately identifying the prostate cancer stage is extremely important. Prostate cancer staging helps to determine the optimal treatment as well as prognosis.

The **TNM** system for describing prostate cancer uses the letters '**T**', '**N**', and '**M**' to signify 'Tumour', 'Nodes', and 'Metastasis'.

The following is the breakdown of exactly what each category in this system means.

Primary tumour (T)

TX: The primary tumour was not or could not be assessed.
T0: There is no evidence of a primary tumour.
T1: The tumour could not be found by examination or with the use of imaging (like ultrasound or an MRI scan), but was incidentally found during a biopsy or surgery.
T1a: The tumour is found in 5% or less of the tissue that was taken.
T1b: The tumour is found in more than 5% of tissue that was taken.
T1c: The tumour was found by needle biopsy after an elevated PSA level.
T2: The tumour is found only within the prostate itself.
T2a: The tumour is found in 50% or less of one lobe.
T2b: The tumour is found in more than 50% of one lobe.
T2c: The tumour is found in both lobes.
T3: The tumour has extended through the capsule that surrounds the prostate.
T3a: The tumour has only gone through the capsule without invading the seminal vesicles.
T3b: The tumour has invaded the seminal vesicles.
T4: The tumour has invaded structures or tissues near the prostate other than the seminal vesicles. These include the bladder neck, the rectum, and the pelvic wall along with other structures.

Nodes (N)

NX: The lymph nodes were not or could not be assessed.
N0: The nodes do not show evidence of cancer.
N1: The nodes show evidence of cancer.

Metastasis (M)

MX: The presence of metastases was not or could not be assessed.
M0: There is no evidence of distant metastasis.
M1: There is evidence of distant metastasis.
M1a: Cancer has been found in lymph nodes far from the prostate.
M1b: Cancer has been found in the bone.
M1c: Cancer has been found in another area of the body.
(About.Com Prostate Cancer; Cancer Research UK).

The following is the Number Staging Method:

Stage I
The prostate cancer is found in the prostate only. Stage I prostate cancer is microscopic; it cannot be felt on a digital rectal examination (DRE) and it is not seen on imaging of the prostate

Stage II
The tumour has grown inside the prostate but has not extended beyond the prostate

Stage III
The cancer has spread outside the prostate, but only barely. Prostate cancer in stage III may involve nearby tissue like the seminal vesicles

Stage IV
The cancer has spread (metastasised) outside the prostate to other tissues. Stage IV prostate cancer commonly spreads to lymph nodes, the bones, liver, or lungs (WebMD).

A New Prostate Cancer Grading System
A newly proposed prostate cancer grading system was released during December 2016. According to the study it can predict mortality risk after radical prostatectomy (RP) among men with Gleason score (GS) 8–10 disease based on both biopsy and RP Gleason scores (Gleason Scores determined on prostate tissue removed during prostatectomy). The study also demonstrated significant differences in all-cause and cancer-specific mortality after RP between men with GS 8 disease and those with GS 9–10 disease.

GS 8 and GS 9–10 disease commonly are lumped into a single high-grade entity (GS 8–10). The new grading system, however, subdivides GS 8–10 into GS 8 and GS 9–10 on the basis of differences in biochemical recurrence after RP.

A team led by Misop Han, MD, of Johns Hopkins Medical Institutions in Baltimore, Maryland evaluated the significance of distinguishing GS 8 and GS 9–10 in terms of long-term survival outcomes for both the preoperative setting using biopsy GS and the postoperative setting with RP GS. The study included 721 men with biopsy GS 8–10 and 1047 with RP GS 8–10. Compared with men who had GS 8 disease, men with GS 9–10 disease had later RP year and higher pathologic stage, Dr Han and his colleagues reported online ahead of print in *European Urology*. Among men with biopsy GS 8–10, 115 died (82 due to PCa) with a median follow-up of 3 years. Of men with RP GS 8–10, 221 died (151 due to PCa) with median follow-up of 4 years.

For both biopsy and RP GS, men with GS 9–10 disease had a significant 2-fold higher risk of PCa-related death than those with GS 8 disease in multivariable analysis, Dr Han's group reported. Men with biopsy and RP GS 9–10 disease had a significant 1.9 times and 1.6 times increased risk of all-cause mortality, respectively, compared with men who had biopsy and RP GS 8 disease.

In a discussion of study limitations, the investigators said they relied on retrospective data collection at a single institution. Consequently, the findings are sensitivity to selection bias and might not be generalizable. The researchers also noted that information about adjuvant and salvage therapy was not included in multivariable analyses.
(Ham, *et al.,* 2016).

Treatment of Prostate Cancer
The main treatments for prostate cancer are surgery, radiotherapy and hormone therapy. Chemotherapy is also sometimes used.

A number of different factors needs to be taken into consideration when deciding on treatment. The most important of these are how fast the cancer is likely to grow and how far it has already grown.

It is generally recommend that treatment is considered individually for every man with prostate cancer.

Patients often query their treatment when they come across other men with prostate cancer who are having different treatment to what they are receiving. They should be informed that it is because they have a different stage or grade of cancer.

- Active Surveillance -The concept of active surveillance, or watchful waiting, has increasingly emerged in recent years as a viable option for men who decide not to undergo immediate surgery or radiation therapy.

  During active surveillance, prostate cancer is carefully monitored for signs of progression. A PSA blood test and digital rectal exam (DRE) are usually administered periodically along with a repeat biopsy of the prostate at one year and then at specific intervals thereafter. If symptoms develop, or if tests indicate the cancer is growing, treatment might be warranted.

  Current estimates indicate that many more men are aggressively treated for prostate cancer than is necessary to save a life from the disease. The challenge has been to identify those men who do not need immediate therapy, which is usually decided based on age, other medical conditions, and cancer factors like the PSA, stage, amount of cancer in the biopsy, and Gleason grade. Research is ongoing to develop biomarkers and additional tests that can better stratify men at risk so that this decision is easier and more accurately informed.

  Today, the man who is ideal for active surveillance has a low grade (Gleason 6 or under), low-risk prostate cancer (low PSA and stage), that appears to be low in volume (small amount of cancer found on biopsy, for example), and who is not eager to undergo therapy right away due to concerns about potency preservation or urinary symptoms.

  Active surveillance might also be a good choice for older men with limited life expectancy. In addition, if a man is currently battling other serious disorders or diseases, such as heart disease, long-standing high blood pressure, or poorly controlled diabetes, his doctors might feel it is in his best interest to hold off on therapy and avoid its potential complications.
  That is because many of the treatment options for prostate cancer can be difficult to endure, and better outcomes are seen in men who are otherwise healthy.

- Surgery - A surgical approach to treating prostate cancer will remove all or part of the prostate. Typically, men with early-stage disease or cancer that's confined to the prostate will undergo radical prostatectomy - removal of the entire prostate gland, plus some surrounding tissue. Other surgical procedures may be performed on men with advanced or recurrent disease.

  The most common types of prostatectomy include:

  Radical Retropubic Prostatectomy - an incision is made in the abdomen and the prostate is removed from behind the pubic bone. The surgeon then stitches the urethra directly to the bladder so urine is able to flow.

Transurethral prostatectomy – transurethral resection of the prostate (TURP) is a type of prostate surgery done to relieve moderate to severe urinary symptoms caused by an enlarged prostate, a condition known as benign prostatic hyperplasia (BPH).

During TURP, a combined visual and surgical instrument (resectoscope) is inserted through the tip of the penis and into the tube that carries urine from the bladder (urethra). The urethra is surrounded by the prostate. Using the resectoscope, the doctor trims away excess prostate tissue that is blocking urine flow and increases the size of the channel that allows one to empty one's bladder.

TURP is one of the most effective options for treating urinary symptoms caused by BPH. To determine whether TURP or another treatment is the right choice, the doctor will consider how severe the patient's symptoms are, what other health problems he has, and the size and shape of the prostate.

Perineal Prostatectomy - A perineal prostatectomy is done through a cut in the area between the testicles and back passage, the perineum.

- Radiation therapy - it involves the killing of cancer cells and surrounding tissues with directed radioactive exposure. The use of radiation therapy as an initial treatment for prostate cancer is described below. Some forms of radiation therapy can also be used in men with advanced or recurrent prostate cancer.

  External Beam Radiation Therapy
  This is the most common type of radiation therapy. CT scans and MRIs are used to map out the location of the tumour cells, and X-rays are targeted to those areas. With 3-D conformal radiotherapy, a computerized program maps out the exact location of the prostate tumours so the highest dose of radiation can reach the cancer cells within the gland.

  Intensity-modulated radiation therapy (IMRT) allows the radiation doctors to modulate, or change, the intensity of the doses and radiation beams to better target the radiation delivered to the prostate, while simultaneously delivering lower doses to the tumour cells that are immediately adjacent to the bladder and rectal tissue. These techniques are always improving, including the use of guidance markers (fiducial markers), which may be able to reduce the risks to the bowel and bladder over time.

  Because the treatment planning with these types of radiation therapy is far more precise, higher—and more effective—doses of radiation can be used with less chance of damaging surrounding tissue. Also, because radiation works slowly, toxicities to the normal surrounding tissues can also develop slowly.

  Many studies have shown that while surgery results in a more immediate loss of erectile function followed by a period of recovery, radiation therapy results in a slower loss of erectile function over time in men who have good erectile function before treatment. By the end of five years, the risks of erectile dysfunction appear to be fairly similar in men who have chosen radiation or surgery.

Regardless of the form of external radiation therapy, treatment courses usually run five days a week for about seven or eight weeks, and are done on an outpatient basis.

- Proton Therapy

  The advantage of using protons over other external beam sources is precision. Protons of energetic particles can hit a targeted prostate cancer tumour without affecting surrounding tissue. This direct attack on cancerous cells ultimately causes their death, as the cells are particularly vulnerable to attack due to their rapid division.

  Proton treatment is notably valuable for treating localized, isolated, solid tumours before they spread to other tissues and the rest of the body. However, to date, proton beam therapy has never been compared directly to standard IMRT techniques, so we do not truly know if this offers an advantage over standard approaches.

  Issues of cost and access have also hampered wider use. Today's proton-therapy machines take up lots of room, owing to the large magnets that create the energetic particles and the concrete walls needed to shield the radiation.

  The machines also come with a hefty cost—between $25 and $150 million—so only a handful of cancer centres can purchase such equipment. There are currently very few medical institutions with proton machines in the United States.
  As efforts are made to reduce the size of these machines, the cost to build them and the price tag for treatment should also fall—giving cancer patients more accessibility to this treatment option. A machine now being developed by researchers at Lawrence Livermore National Laboratory is expected to be a fifth of the size and cost of the machines in use today.

- Brachytherapy

  With brachytherapy, tiny metal pellets containing radioactive iodine or palladium are inserted into the prostate via needles that enter through the skin behind the testicles. As with 3-D conformal radiation therapy, careful and precise maps are used to ensure that the seeds are placed in the proper locations.

  Over the course of several months, the seeds give off radiation to the immediate surrounding area, killing the prostate cancer cells. By the end of the year, the radioactive material degrades, and the seeds that remain are harmless.

  Compared with external radiation therapy, brachytherapy is less commonly used, but some patients prefer this option primarily because it doesn't require daily visits to the treatment centre. Side effects can include erectile dysfunction, urinary frequency and obstruction, and rarely rectal injury.

  The American Society of Clinical Oncology (ASCO) and Cancer Care Ontario have issued a joint clinical practice guideline update on the use of brachytherapy for prostate cancer patients.

  The main updated recommendations are as follows:

Among all eligible patients with low-risk disease who require or who select to undergo active treatment, low-dose brachytherapy alone, External Beam Radiation Therapy (EBRT) alone, or (Radical Prostatectomy) RP should be offered. All patients should be counselled about all their treatment options in a balanced, objective manner, preferably from a multidisciplinary team. This recommendation is unchanged from the previous guidelines, because no new data had a bearing on this clinical question.

In the population with intermediate-risk prostate cancer who select EBRT with or without androgen-deprivation therapy (ADT), brachytherapy boost (either low or high dose) should be offered to all eligible patients. In the low-intermediate risk group (Gleason 7, prostate-specific antigen, <10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL) low-dose brachytherapy alone can be offered as monotherapy. For eligible patients with high-risk disease who are being treated with EBRT and ADT, brachytherapy boost (LDR or high–dose rate) should be offered.

Some patients in the intermediate- or high-risk groups may be ineligible for brachytherapy, and ADT may be given in neoadjuvant, concurrent, and/or adjuvant settings at physician discretion. Of note, the addition of neoadjuvant ADT could induce cytoreduction of prostate volume sufficient to allow brachytherapy.

For patients receiving low-dose brachytherapy, ^{125}I and ^{103}Pd are each reasonable isotope options, but no recommendation could be made for or against using ^{131}Cs or high-dose brachytherapy.

Patients who opt for brachytherapy should only be treated at centres that follow strict quality-assurance standards, the document emphasises.

It also notes that there may be increased genitourinary toxicity after brachytherapy compared with EBRT alone. Also, the authors note that it "cannot be determined whether there is an overall or cause-specific survival advantage for brachytherapy compared with EBRT alone, because none of the trials were designed or powered to detect a meaningful difference in survival outcomes."

Patients should be encouraged to participate in clinical trials that are evaluating novel or targeted therapies, the authors add.
(Medscape).

- Hormone Therapy - Prostate cancer cells are like other living organisms—they need fuel to grow and survive. Because the hormone testosterone serves as the main fuel for prostate cancer cell growth, it’s a common target for therapeutic intervention in men with the disease.

  Hormone therapy, also known as androgen-deprivation therapy or ADT, is designed to stop testosterone from being released or to prevent it from acting on the prostate cells. Although hormone therapy plays an important role in men with advancing prostate cancer, it is increasingly being used before, during, or after local treatment as well.

  The majority of cells in prostate cancer tumours respond to the removal of testosterone. But some cells grow independent of testosterone and remain

unaffected by hormone therapy. As these hormone-independent cells continue to grow unchecked, hormone therapies have less and less of an effect on the growth of the tumour over time.

For this reason, hormone therapy is not a perfect strategy in the fight against prostate cancer, and it does not cure the disease. It also carries some unwanted toxicities. But it remains an important step in the process of managing advancing disease, and it will likely be a part of every man's therapeutic regimen at some point during his fight against recurrent or advanced prostate cancer.

The timing of when to start hormone therapy once the PSA begins to rise is an individual decision and one that should be discussed with your doctor.

The most common types of hormone therapy are described below. Although each option is effective at controlling prostate cancer growth, the loss of testosterone confers significant side effects in nearly all men. These side effects range from hot flashes and loss of bone density to mood swings, weight gain, and erectile dysfunction. Learn more about the side effects of hormone therapy—and how to manage or minimize them.

- Orchidectomy **-** About 90% of testosterone is produced by the testicles. So orchidectomy (the surgical removal of the testicles) is an effective solution to blocking testosterone release. This approach has been used successfully since the 1940s. Because it's permanent and irreversible, most men opt for drug therapy instead.

  For those who choose this option, the procedure is typically done on an outpatient basis in the urologist's office. Recovery tends to be rather quick and no further hormone therapy is needed, making it a very attractive choice for someone who prefers a low-cost, one-time procedure.

- LHRH Agonists **-** LHRH, or luteinizing-hormone releasing hormone, is one of the key hormones released by the body before testosterone is produced. (Note that LHRH is sometimes called GnRH, or gonadotropin-releasing hormone.)

  Blocking the release of LHRH through the use of LHRH agonists or LHRH analogues is one of the most common hormone therapies used in men with prostate cancer. Drugs in this class, including leuprolide (Eligard, Lupron, and Viadur), goserelin (Zoladex), and triptorelin (Trelstar), are given in the form of regular shots: once a month, once every three, four, or six months, or once per year.

- LHRH Antagonists **-** A newer class of medications can block LHRH (GnRH) from stimulating testosterone production without causing an initial testosterone surge. This class includes degarelix, which is given monthly to men as an alternative to orchiectomy or LHRH agonists.

- Anti-androgens - LHRH agonists cause what is known as a "flare" reaction because of an initial transient rise in testosterone over the first three weeks after the shot is

given. This can result in a variety of symptoms, ranging from bone pain to urinary frequency or difficulty. Fortunately, this can be prevented.

- Anti-androgens such as bicalutamide (Casodex), flutamide (Eulexin), and nilutamide (Nilandron) can help block the action of testosterone in prostate cancer cells. They are often added to the LHRH agonist to prevent flare reactions.

  Although the sexual side effects of the anti-androgens when given alone are typically far fewer compared with the LHRH agonists, anti-androgens might not be as effective as orchiectomy or LHRH agonists, and they are not the optimal choice for men with documented metastatic prostate cancer.

  When used in combination with LHRH agonists, anti-androgens tend to increase the risk of hot flashes and breast tenderness, and they can rarely result in liver injury. Your liver function tests should be monitored while you take these medications.

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

  Newer hormonal medications that inhibit the synthesis of androgen (abiraterone) and block androgen receptor signalling (enzalutamide) are now FDA-approved for the treatment of metastatic prostate cancer after treatment with chemotherapy, however they are still under investigation for use earlier in the disease, like when the PSA begins to rise or before chemotherapy.

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

  For a man starting hormonal therapy, visits are usually timed with the LHRH injection, along with PSA and other lab check-ups such as the testosterone levels and liver and kidney function tests. There is a wide variety of practice patterns, but typically, checking bone mineral density before starting hormonal therapy and once per year to assess the loss of bone density is reasonable given that there are medications that can be used to reduce the risk of fracture.

  The most common types of initial hormone therapy are described above. These include orchiectomy, LHRH agonists or antagonists, and anti-androgens.

  These initial hormone therapies are typically effective for only a few years. After this time, the hormone-independent cells eventually become strong enough that hormone therapies will have less and less of an effect on the growth of the tumour. However, because the hormone sensitive cells aren't actually eradicated, a number of 'secondary' hormone approaches can be used to keep the tumour from spreading.

  For many men who were using an antiandrogen in combination with an LHRH agonist, stopping the antiandrogen, or *antiandrogen withdrawal*, is the most common first step in secondary hormone therapy. About 10-30% of men will experience this

anti-androgen withdrawal, which lasts on average 3-5 months, during which time additional therapies are not needed. However, inevitably, additional therapies will be needed even if this withdrawal response occurs. *Switching* to a different antiandrogen might also be able to offer an extra few months of benefit before other therapeutic approaches are required.

Another option is to block the release of testosterone from the adrenal glands, small organs that sit on top of the kidneys. Only about 10% of the circulating testosterone is produced by these two glands, so few therapeutic interventions focus on them until it becomes important that every last bit of the hormone is removed. The commonly used drugs used for this purpose,*ketoconazole* and the newer agent abiraterone acetate (Zytiga), are typically administered in conjunction with steroids to avoid the effects seen when the adrenal glands are shut down. Abiraterone acetate plus low-dose steroids has been shown to prolong life when given to men after chemotherapy with docetaxel. A large study evaluating the role of abiraterone acetate prior to chemotherapy has been completed, but the results are not yet available. While awaiting the results of this study, the standard practice is to offer abiraterone treatment after chemotherapy or in men who are not candidates for chemotherapy. Although this medication is generally well-tolerated, side effects may include fatigue, high blood pressure, and electrolyte or liver abnormalities and patients need to be monitored regularly.

- Enzalutamide - In August 2012, the FDA approved enzalutamide (Xtandi) for the treatment of men with castration-resistant metastatic prostate cancer who had disease progression after docetaxel chemotherapy. Similar to but more effectively than the anti-androgens, enzalutamide blocks the androgen receptor. Approval was based on the results of the AFFIRM randomized, phase 3, placebo-controlled trial in which both survival and quality of life were improved with enzalutamide treatment. Side effects are mild but include fatigue, diarrhea, hot flushes, headache, and very rarely seizures. Importantly, enzalutamide treatment does not require simultaneous steroid treatment and therefore the steroid side effects can be avoided. Thus, enzalutamide is a new treatment option for men in the post-docetaxel metastatic CRPC setting and is also a reasonable choice in men who are not candidates for chemotherapy. Evidence to support the use of enzalutamide in the pre-docetaxel setting will be based on the results of the PREVAIL study, which are not yet available.

- Chemotherapy - The term ‘chemotherapy’ refers to any type of therapy that uses chemicals to kill or halt the growth of cancer cells. The drugs work in a variety of ways, but are all based on the same simple principle: stop the cells from dividing and you stop the growth and spread of the tumour.
-

  Until recently, chemotherapy was used only to relieve symptoms associated with very advanced or metastatic disease. With the publication of two studies in 2004 showing that the use of docetaxel (Taxotere) can prolong the lives of men with prostate cancer that no longer responds to hormone therapy, more and more doctors are recognising the potential benefits of chemotherapy for the men they treat with advanced prostate cancer.

Building on these successes, there are now dozens of clinical trials studying various combinations of chemotherapy drugs, some using new mixes of older drugs and some using newer drugs. Some trials are looking to find a chemotherapy regimen that's more tolerable or more effective than docetaxel in men with metastatic disease, others are looking to find a chemotherapy regimen that can delay the onset of metastases, and still others are seeking to improve upon the results with docetaxel by adding to it other novel agents and testing the combination.

In addition, several agents are approved or widely available for use in prostate cancer, including estramustine and mitoxantrone. Estramustine (Emcyt) is an oral medication with hormonal and chemotherapeutic properties that has anti-cancer activity, and can be safely combined with other chemotherapies. Mitoxantrone (Novatrone) is a chemotherapy agent given intravenously every three weeks and is known to delay and reduce pain from prostate cancer metastasis from earlier studies. It remains an effective weapon against prostate cancer. However, it does have a risk of congestive heart failure which limits its use to generally under 10 cycles, and regular heart monitoring is necessary.

Paramount in all researchers' minds is a way to maximize benefit while minimizing side effects. Chemotherapy, like all powerful drugs, can take a toll on the body.

- Other treatment options - Surgery and radiation therapy remain the standard treatment for localized prostate cancer, but other, less popular treatment options might be beneficial as well. As time goes on and the benefits of these treatment options are further explored, it's possible that they will move more into the mainstream. For now, though, none are seen as standard treatments for localized prostate cancer.

Cryotherapy - Cryotherapy, also known as cryosurgery or cryoablation, has been around for years, but until a few years ago, it was rarely used. With this approach, probes are inserted into the prostate through the perineum (the space between the scrotum and the anus), and argon gas or liquid nitrogen is delivered to the prostate, literally freezing to death the prostate cells and any prostate tumours. (Review the roles of the prostate and the surrounding organs in the About the Prostate section.)

Over the years, a number of modifications were made to avoid freezing damage to the nearby structures, but the rates for both erectile and urinary dysfunction remain high, and data on long-term outcomes are limited.

Cryotherapy is also used as a secondary local therapy in men who underwent radiation therapy as initial treatment for early-stage prostate cancer. Note that men with more well-confined disease tend to fare better, while those who received hormone therapy in addition to radiation therapy tend to fare worse. Side effects of this focal therapy include further urinary or sexual problems such as urinary stricture, erectile dysfunction, and urgency. Rarely, cryotherapy can result in injury to surrounding tissues such as the rectum or bladder given the proximity of these structures to the prostate bed.

High-Intensity Focused Ultrasound - High-intensity focused ultrasound, or HIFU, works in exactly the opposite way compared with cryotherapy: with HIFU, the

prostate cells are heated to death. A probe is inserted into the rectum, from which very high-intensity ultrasound waves are delivered to the target area. Although this technique remains experimental in the United States, it's been used in Europe for a number of years with a fair amount of success. Side effects of HIFU are similar to those discussed above for cryotherapy and depend on the skill and experience of the surgeon using this technique.

Primary Hormone Therapy - Prostate cancer cells are like other living organisms—they need fuel to grow and survive. Because the hormone testosterone serves as the main fuel for prostate cancer cell growth, it's a common target for therapeutic intervention in men with the disease. Hormone therapy, also known as androgen-deprivation therapy or ADT, is designed to stop testosterone from being released or to prevent it from acting on the prostate cells.

Although hormone therapy plays an important role in men with advancing prostate cancer, it is also increasingly being used before, during, or after local treatment. In some cases, hormone therapy may be used in conjunction with radiation therapy. If so, treatment with ADT is gernally given before, during and after radiation therapy in the form of an LHRH agonist. LHRH, or luteinizing hormone releasing hormone, is one of the key hormones involved in the production of testosterone. This medicine works through a complicated feedback loop to lower the body's testosterone. Note that LHRH is sometimes called GnRH, or gonadotropin-releasing hormone. Although there is little, if any, data to show that hormone therapy alone is an effective treatment strategy for men with localized prostate cancer, it is increasingly being used in this setting.

Because it is not invasive, it is possible that the therapy is seen as a middle ground between active surveillance and local therapy. For men who are not good candidates for surgery or radiation, and who require immediate therapy, primary hormonal therapy is a reasonable option. However, hormonal therapy has a long list of side effects, and thus, the main question is whether therapy can be safely deferred in men who are not candidates for immediate surgery or radiation. Primary hormonal therapy is also a reasonable option in men who have metastatic disease (cancer spread beyond the prostate) when the diagnosis of prostate cancer is made. In these men, hormonal therapy will shrink the prostate gland and cancer and may delay any need for local therapy.

- Emerging Therapies - In laboratories around the world, researchers are busy identifying new drugs and treatment approaches that might prove beneficial to men with prostate cancer. Most of these investigational agents are being tested in men with advanced prostate cancer: therapy options for men at this stage of disease may not be effective enough to halt progression of the disease, and men are typically affected by side effects from the disease and/or the medications that they're taking. It's therefore the perfect stage at which to test out new drugs because any improvement will likely be rapidly noticed and much appreciated.

- Targeted Therapies - Chemotherapy drugs can play an important role in improving the lives of men with advanced prostate cancer, but they often don't distinguish between tumour cells and healthy cells to a high degree and can kill off some normal

cells along the way. So-called targeted therapies, by contrast, are drugs that are specifically designed to interfere with the way cancer cells grow, with the way cancer cells interact with each other, and/or with the way that the immune system interact with the cancer without damaging a man's normal cells.

There are a number of different kinds of targeted therapies being investigated for prostate cancer. As of yet, none have been approved by the FDA for use in prostate cancer, but the excitement generated by some of the early studies have led many researchers to believe that it's only a matter of time before a targeted therapy is found that can result in better outcomes overall.

All cells in the body, including cancer cells, rely on a complex communication system to know when to grow, when to divide, and when to die. This system uses specialized proteins, fats, and other substances to tell the different cells or parts of cells how to act. Over the years, cancer researchers have been studying ways to interfere with the signalling system that regulates the growth of cancer cells.

So far, interfering with cellular signalling to halt cancer cell growth hasn't yet proven to be a very effective strategy in prostate cancer. But in the process of learning which drugs might work and why, researchers found that the strategy of adding a 'targeted therapy' to other effective drugs in order to see better results than with either drug alone is an important part of cancer research. The idea is to exploit the synergy between the two drugs, or the ways in which the two drugs might work together to fight off the cancer.

(Cancer Research UK; Prostate Cancer Foundation; National Cancer Institute; Prostate Cancer UK).

PROSTATE CANCER TREATMENT REGIMENS

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Castration-Recurrent Prostate Cancer[1]

First-Line Therapy[1]

Note: All recommendations are Category 2A unless otherwise indicated.

No Visceral Metastases

REGIMEN	DOSING
Enzalutamide (Category 1)[2-4]	Enzalutamide 160mg (four 40mg capsules) orally daily with or without food; prednisone can be given concurrently but is not required.
Abiraterone acetate + prednisone (Category 1)[5-8]	Abiraterone 1,000mg orally once daily on an empty stomach, plus prednisone 5mg orally twice daily.

PROSTATE CANCER TREATMENT REGIMENS

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

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Castration-Recurrent Prostate Cancer[1]

First-Line Therapy[1]

Note: All recommendations are Category 2A unless otherwise indicated.

No Visceral Metastases

Docetaxel + prednisone (Category 1)[9,10]	**Day 1:** Docetaxel 75mg/m^2 IV once every 3 weeks + prednisone 5mg orally twice daily. Repeat for up to 10 cycles if tolerated.
Radium-223 (for symptomatic bone metastases) (Category 1)[11,12]	Radium-223 50kBq/kg every 4 weeks for 6 injections.

Visceral Metastases

Docetaxel + prednisone (Category 1)[9,10]	**Day 1:** Docetaxel 75mg/m^2 IV once every 3 weeks + prednisone 5mg orally twice daily. Repeat for up to 10 cycles if tolerated. Addition of estramustine to this regimen is not recommended.
Enzalutamide (Category 1)[2-4]	Enzalutamide 160mg (four 40mg capsules) orally daily with or without food; prednisone can be given concurrently but is not required.
Abiraterone acetate + prednisone[5-8]	Abiraterone 1,000mg orally once daily on an empty stomach, plus prednisone 5mg orally twice daily.
Mitoxantrone + prednisone[9,10]	**Day 1:** Mitoxantrone 12–14mg/m^2 IV every 3 weeks + prednisone 10mg orally daily or 5mg twice daily. Repeat for up to 10 cycles if tolerated.

Subsequent Therapy[1]

No Visceral Metastases

Prior Therapy Enzalutamide/Abiraterone

Docetaxel + prednisone (Category 1)[9,10]	**Day 1:** Docetaxel 75mg/m^2 IV once every 3 weeks + prednisone 5mg orally twice daily. Repeat for up to 10 cycles if tolerated.
Abiraterone acetate + prednisone[5-8]	Abiraterone 1,000mg orally once daily on an empty stomach, plus prednisone 5mg orally twice daily.
Enzalutamide[2-4]	Enzalutamide 160mg (four 40mg capsules) orally daily with or without food; prednisone can be given concurrently but is not required.
Radium-223 (for	Radium-223 50kBq/kg every 4 weeks for 6 injections.

PROSTATE CANCER TREATMENT REGIMENS

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Castration-Recurrent Prostate Cancer[1]

First-Line Therapy[1]

Note: All recommendations are Category 2A unless otherwise indicated.

No Visceral Metastases	
symptomatic bone metastases) (Category 1)[11,12]	
Sipuleucel- T (if no or minimal symptoms, no liver metastases, life expectancy >6 months, and an ECOG score of 0 or 1)[13,14*]	Sipuleucel-T three complete doses (50 million autologous CD54+ cells), given at 2-week intervals (range 1–15 weeks).
Prior Therapy Docetaxel	
Enzalutamide (Category 1)[2-4]	Enzalutamide 160mg (four 40mg capsules) orally daily with or without food; prednisone can be given concurrently but is not required.
Abiraterone acetate + prednisone (Category 1)[5-8]	Abiraterone 1,000mg orally once daily on an empty stomach, plus prednisone 5mg orally twice daily.
Radium-223 (for symptomatic bone metastases) (Category 1)[11,12]	Radium-223 50kBq/kg every 4 weeks for 6 injections.
Cabazitaxel + prednisone (Category 1)[15-17]	**Day 1:** Cabazitaxel 25mg/m^2 IV every 3 weeks + prednisone 10mg orally daily or 5mg twice daily throughout cabazitaxel treatment (starting doses are reduced by 5 mg/m^2 and 10 mg/m^2 for mild and moderate hepatic impairment, respectively). Repeat for up to 10 cycles if tolerated.
Sipuleucel-T (if no or minimal symptoms, no liver metastases, life expectancy >6 months, and an ECOG score of 0 or 1)[13, 14*]	Sipuleucel-T three complete doses (50 million autologous CD54+ cells), given at 2-week intervals (range 1–15 weeks).
Docetaxel rechallenge[9,10]	**Day 1:** Docetaxel 75mg/m^2 IV once every 3 weeks + prednisone 5mg orally twice daily. Repeat for up to 10 cycles if tolerated.
Mitoxantrone + prednisone[9,10]	**Day 1:** Mitoxantrone 12mg/m^2 IV every 3 weeks + prednisone 10mg orally daily or 5mg twice daily. Repeat for up to 10 cycles if tolerated.
Visceral Metastases	

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Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

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Castration-Recurrent Prostate Cancer[1]

First-Line Therapy[1]

Note: All recommendations are Category 2A unless otherwise indicated.

No Visceral Metastases

Prior Therapy Enzalutamide/Abiraterone	
Docetaxel + prednisone (Category 1)[9,10]	**Day 1:** Docetaxel 75mg/m^2 IV once every 3 weeks + prednisone 5mg orally twice daily. Repeat for up to 10 cycles if tolerated.
Abiraterone acetate + prednisone[5-8]	Abiraterone 1,000mg orally once daily on an empty stomach, plus prednisone 5mg orally twice daily.
Enzalutamide[2-4]	Enzalutamide 160mg (four 40mg capsules) orally daily with or without food; prednisone can be given concurrently but is not required.
Prior Therapy Docetaxel	
Enzalutamide (Category 1)[2-4]	Enzalutamide 160mg (four 40mg capsules) orally daily with or without food; prednisone can be given concurrently but is not required.
Abiraterone acetate + prednisone (Category 1)[5-8]	Abiraterone 1,000mg orally once daily on an empty stomach, plus prednisone 5mg orally twice daily.
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Docetaxel rechallenge[9,10]	**Day 1:** Docetaxel 75mg/m^2 IV once every 3 weeks + prednisone 5mg orally twice daily. Repeat for up to 10 cycles if tolerated.
Mitoxantrone + prednisone[9,10]	**Day 1:** Mitoxantrone 12mg/m^2 IV every 3 weeks + prednisone 10mg orally daily or 5mg twice daily. Repeat for up to 10 cycles if tolerated.

General treatment notes:

- Encourage men with advanced prostate cancer to participate in clinical trials and refer early to a medical oncologist.
- Reserve systemic chemotherapy for men with castration-resistant metastatic prostate cancer except when enrolled in a clinical trial.

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Castration-Recurrent Prostate Cancer[1]

First-Line Therapy[1]

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No Visceral Metastases

- Secondary hormone therapy (eg, antiandrogens, antiandrogen withdrawal, ketoconazole, corticosteroids) is also an option for patients with castration-resistant prostate cancer.
- All prostate cancer patients should receive best supportive care throughout treatment.

* The maximum dosing interval has not been established.[13]

(Cancer Therapy Advisor).

Treatment of Advanced Prostate Cancer

Men with advanced prostate cancer might be able to avoid chemotherapy by taking an additional anti-testosterone pill along with standard hormone therapy, a pair of new clinical trials show. The drug, abiraterone (Zytiga), lowered patients' risk of death by nearly 40 percent when added to standard androgen deprivation therapy, both studies found. Abiraterone also appeared to more than double the average time it took for a man's prostate cancer to progress, one of the studies reports.

Doctors currently combine the chemotherapy drug docetaxel with hormone therapy to treat patients with advanced prostate cancer, where the cancer has spread to the bone or other parts of their body.

Abiraterone now offers a reasonable alternative to chemotherapy for these men.
(Pal, *et al*., 2017).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may

also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects.

Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial
The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials
In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over
After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Questions that Patients should ask their Health Professional
It is important for health professionals to have honest, open discussions with their patients about prostate cancer. Some questions from patients pertaining to prostate cancer that every health professional should be able respond to:

- What type of prostate cancer do I have?
- What are the chances that the cancer has spread beyond my prostate? If so, is it still curable?
- What further tests (if any) do you recommend, and why?
- Are there other types of doctors I should talk to before deciding on treatment?
- What is the clinical stage and Gleason score (grade) of my cancer? What do those mean to me? Does this make me a low-risk, intermediate-risk or high-risk patient?
- What is my expected survival rate based on clinical stage, grade, and various treatment options?
- Should I consider active surveillance as an option? Why or why not?
- Do you recommend a radical prostatectomy or radiation therapy? Why or why not?
- Should I consider laparoscopic or robot-assisted prostatectomy?
- What types of radiation therapy might work best for me?
- What other treatment(s) might be right for me? Why?
- Will I have to have my testicles removed? If so, why? What will the short and long term effects be?
- What risks or side effects should I expect from my treatment options?
- What are the chances that I will have problems with incontinence or impotence?
- What are the chances that I will have other urinary or rectal problems?
- How quickly do I need to decide on treatment?
- What should I do to be ready for treatment?
- How long will treatment last? What will it be like? Where will it be done?
- How would treatment affect my daily activities?
- What are the chances my cancer will come back with the treatment plans we have discussed? What would be our next step if this happened?
- What type of follow-up will I need after treatment?
- Where can I find more information and support?
- What is my risk of recurrence after surgery or radiation based on my Gleason score, PSA, rate of PSA rise, and stage?
- What is my risk of progression over time without therapy? Do I need immediate therapy?
- Are you comfortable with me exploring other treatment options and speaking with other specialists (urologists, radiation oncologists, medical oncologists) before deciding upon a final plan of action?
- What are the common side effects of the treatments recommended and when do they occur?
- How many men with prostate cancer do you treat (with surgery, radiation, etc) per year?
- What should I do to keep my body and mind healthy now that I have been diagnosed with prostate cancer?
- Based upon what we know today, what is the chance that my cancer spread beyond the prostate? What is the cure rate for this type of cancer?
- Are there additional tests that we can do to gain the most complete understanding of the stage and aggressiveness of my cancer?
- What are all of the treatment options for this stage of cancer?
- What are the benefits of the type of therapy you are recommending?
- What are the drawbacks/side effects of this type of therapy?
- Will I have problems with sexual function?
- Will I have other urinary or rectal problems?
- What other treatment(s) might be appropriate and why?

- Is my cancer likely to come back based on what you know today?
- What can I do to improve the success of my therapy?
- What kind of follow-up can I expect after treatment?
- Should I join a clinical trial?
- If I am going to be operated, which surgical technique will be used? Open, laparoscopic, robotic?
- Based on your experience, why is this the right approach for me?
- Do you plan to employ a nerve-sparing technique with the aim of conserving my ability to get an erection following surgery?
- What level of success have you had in preserving potency (ability to get an erection) in your patients following surgery?
- What about preserving urinary continence (bladder control)?
- What will you do if you find cancer outside of my prostate during the surgery?
- Will that change my prognosis and future treatment?
- Do I need to be concerned about blood loss during the surgery? Should I store my blood or get my family and friends to donate blood in case it is needed?
- What can I expect following the surgery in terms of recovery time? How long will it be before I can return to my normal activities?
- What are the likely or possible side effects of the surgery, both short-term and long-term?
- What will we do to monitor my prostate cancer following the surgery?
- If I am given radiation therapy, which radiation technique will be used? Seeds, external beam, intensity-modulated radiation therapy (IMRT)?
- Based on your experience, why is this the right approach for me?
- How will this procedure precisely target the cancer tissue but leave the normal tissue unharmed?
- Are there specific radiation therapy approaches that we should discuss or consider, such as IMRT or brachytherapy? What about special markers to help guide the radiation dose in real time to possibly prevent toxicity?
- What dose of radiation will you be using and how/why did you select that dose of radiation?
- How often will I need to come into the clinic for treatments?
- Do you recommend that we initiate androgen deprivation therapy ("hormone therapy") before the radiation treatments? Why or why not?
- What can I expect following the treatments in terms of recovery time? How long will it be before I can return to my normal activities?
- Are there delayed side effects that might appear over time?
- What will we do to monitor my prostate cancer following the radiation?
- What treatment options are there if my cancer progresses?
- How will I be followed? What will be the frequency of PSA tests, rectal examinations, and repeat biopsies?
- When will a repeat biopsy be considered and how will the biopsy information be used to decide on surgery or radiation?
- Who will be the doctor to follow me during this time?
- Are there dietary or lifestyle changes that I can make that can slow prostate cancer growth or that may allow my body to be more healthy to fight this prostate cancer?
- I was told that cannabis oil is effective in treating prostate cancer. Should I consider using cannabis oil? Why or why not?

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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