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# EPIDEMIOLOGY AND DIAGNOSTIC TOOLS TO DETECT AND DIAGNOSE PROSTATE CANCER

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## *Abstract*

*One of the cancers that affects men and has a major impact on the rising death rates among men worldwide is prostate cancer. Prostate cancer patients may have localized or advanced disease at presentation. Our goal in this study is to present a comprehensive picture of prostate cancer, covering its epidemiology and several diagnostic techniques.*

*Prostate-specific antigen (PSA) testing, transrectal ultrasound (TRUS), magnetic resonance imaging (MRI), prostate biopsy, Positron emission tomography (PET) scan, risk stratification bioassay test, germline testing, digital rectal exam (DRE), and single-cell RNA-sequencing (scRNA-seq) were among the techniques we covered. For clinical and patient care, prostate cancer (PCa) diagnosis and appropriate staging are essential. Thanks to extensive medical research and development, sensitive and advanced diagnostic instruments are now available. Prostate-specific antigen (PSA) blood testing and rectal examination continue to be the mainstays of screening, while multiparametric magnetic resonance imaging (mpMRI) is used for local staging. In order to better detect clinically significant PCa and identify patients who need targeted biopsies, recent developments in mpMRI, PET, and MRI have led to standardized interpretation and greater prescription by doctors. Other types that are becoming increasingly important, particularly to identify the recurrent rate of cancer, include germline testing, risk stratification bioassay testing, and single-cell RNA-sequencing (scRNA-seq). The combined use of these technologies will assist patients and clinicians in selecting the most suitable and individualized course of treatment for this highly variable condition and also make early diagnosis achievable.*

***Key words:*** *Prostate cancer, Epidemiology in India, MRI, PET scan, PSA, scRNA-seq.*

## BACKGROUND:

The most prevalent solid cancer in men worldwide is prostate cancer. In 2022, there were a projected 268,490 new cases of prostate cancer in the United States. An estimated 34,500 people have died from prostate cancer [Siegel, R.L., 2022]. The two mainstays of treatment for localized illness are surgery and radiation. The most common medical treatments for recurrent or metastatic illness are chemotherapy, androgen signaling inhibition (ARSI), and androgen deprivation therapy (ADT). Most patients, however, develop castration resistance, which is linked to a poor prognosis. Beneath the bladder is the male auxiliary reproductive organ, the prostate. Its primary purpose is to maintain the viability of the sperm and to supplement the vital secretions in semen. The central, transitional, and peripheral parts of the human prostate are separated in adults. Adenocarcinomas account for almost 95% of occurrences of prostate cancer (PCa), with ductal origins being rare and acinar origins being the most common [Bray, F.; 2018]. Nearly 80% of prostate adenocarcinomas originate from the peripheral luminal or basal (less common) epithelial cells, which make up more than 70% of the prostate's total tissue. About six out of 10 occurrences of PCa occur in men over 65.

PCa is the second most common solid-organ cancer in males, behind lung cancer [Bray, F.; 2018]. It is also a serious health concern, with 358,989 recorded deaths worldwide and around 1.3 million new cases diagnosed in 2018 [Rawla, P., 2019]. Currently, the disease affects about 10 million men worldwide, 700,000 of whom have a metastatic form [Sandhu, S.; 2021]. Despite the fact that PCa is typically detected early, the treatment's risk-benefit ratio is still unknown. The substantial morbidity from the existing style of therapy makes it one of the most contentious areas of medicine. Clinicians often view the treatment workup of PCa as a lengthy process due to the disease's lengthy history and the unpredictability of each patient's clinical progress.

The complicated cancer known as PCa has a wide range of death and morbidity rates. Adenocarcinomas with an acinar origin have a significantly better prognosis than those with a ductal origin in PCa patients. Prostate-limited localized prostate cancer accounts for about 80% of male PCa diagnoses [Siegel, R.L.; 2018]. Men with localized

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PCa have a 99% chance of living for more than ten years if they receive an early diagnosis [Rebello, R.J., 2021]. The majority of men with PCa must follow a personalized treatment plan for their slow-growing, frequently even indolent cancer in order to survive; however, for a number of other men, relapsed PCa after a definitive treatment plan may be aggressive and, in rare instances, may not respond to the current standard of care.

According to Siegel (2018), 15% of males with PCa are diagnosed with locoregional metastases, while 5% are identified with distant metastases, which are frequently seen in numerous sites. When males are diagnosed with late-stage PCa (far metastases), their overall five-year survival rate is only 30%. Every year, metastatic PCa causes over 400,000 fatalities, and by 2040, this mortality rate is predicted to have doubled or more [Sandhu, S.; 2021]. Additionally, it is predicted that a comparable proportion of males will experience treatment-related morbidity for over ten years following diagnosis [Sandhu, S.; 2021]. At a secondary location, the metastasized PCa cells may remain dormant in the tumor microenvironment for an extended period of time.

For a considerable amount of time, the metastasized PCa cells may remain dormant in the tumor microenvironment at a secondary site. PCa metastasis is mainly linked to hematogenous dissemination to the bone marrow stroma in the axial skeleton and/or spread to the locoregional lymph nodes. Bone tissue contains about 80% of distant metastatic lesions [Berish, R.B, 2018]. In rarer instances, PCa metastasis is linked to the dissemination to distant visceral locations. The majority of individuals who develop metastatic prostate cancer eventually develop castration-resistant prostate cancer (CRPC), which is resistant to androgen deprivation therapy (ADT). The primary causes of PCa morbidity and mortality are these characteristics. Eventually, metastatic CRPC (mCRPC) develops into therapy- and castration-resistant PCa (t-CRPC), which is regarded as an end-stage disease and for which there is no longer any viable treatment [Ritch, C.R, 2016].

**1. Epidemiology:**

With an expected 1.4 million diagnoses and 375,000 deaths globally in 2020, prostate cancer (PCa) is the second most frequent malignancy in men [Culp, M.B, 2020]. It is the third leading cause of cancer-related mortality for males in Europe and the most common cancer diagnosed in men [Bell, K.J., 2015]. According to an SR of autopsy studies, the prevalence of PCa was 5% (95% CI: 3–8%) at age <30 years. It increased by 1.7 (1.6–1.8) odds ratios (OR) every decade to 59% (48–71%) by age >79 years [Bell, K.J., 2015]. Men from different ethnic backgrounds and geographical locations had varying rates of autopsy-detected PCa (e.g., 83% in white US males vs. 41% in Japan at age 71–80) [Haas, G.P, 2008].

The rate of prostate-specific antigen (PSA) testing and the screening recommendations of (international) organizations are the main causes of the even more noticeable variance in the prevalence of PCa diagnosis across different geographic locations [Fleshner, K.,, 2017].

Age-standardized rates [ASR] per 100,000 are highest in Western and Northern Europe (ASRs of 94.9 and 85, respectively), and in Australia/New Zealand and Northern America (ASRs of 111.6 and 97.2, respectively). With ASRs of 10.5 and 4.5, respectively, the incidence is low in Eastern and South-Central Asia but is on the rise [IARC, 2012]. Although they were modest, rates in Eastern and Southern Europe have been steadily rising. Incidence is influenced by region, ethnicity, and population age in addition to PSA testing. Although mortality rates are generally high in populations of African descent (e.g., Caribbean: ASR of 29 and Sub-Saharan Africa: ASRs ranging between nineteen and fourteen), intermediate in the USA, and very low in Asia (South-Central Asia: ASR of 2.9), there is comparatively less variation in mortality rates globally [IARC, 2012]. Although the extent of the decline differs by country, PCa-related mortality has declined in the majority of Western countries.

According to the Global Cancer Observatory (GLOBOCAN) estimates, there were 19.3 million incident cancer cases worldwide for the year 2020 [Sung H, 2021]. India ranked third after China and the United States of America. GLOBOCAN predicted that cancer cases in India would increase to 2.08 million, accounting for a rise of 57.5 per cent in 2040 from 2020 [Sung H, 2021]. Planning, monitoring and evaluation of cancer control activities requires recent statistics in any region. This is usually achieved through the Population-Based Cancer Registries (PBCRs). Cancer is not a nationally notable disease in India. Thus, the data collection from PBCRs involves active retrospective data abstraction, laborious and a complex process of analysis and reporting. Trained registry staff typically goes to different resource centers (hospitals, vital statistics departments and diagnostic laboratories) for collecting data on a standardized core form [Siegel RL, 2022]. This delays the process of real-time reporting and bringing out the most recent cancer statistics. Globally, there is usually a lag of 2-4 yr between actual cancer registry data and the publication of results (e.g. US cancer registry, GLOBOCAN) [Bray F, 2017]. Thus, providing estimates at periodic intervals is the best way for informing cancer prevention and control programmes. Hence, efforts to provide timely cancer estimates based on the recently available data for formulating appropriate cancer control measures are proposed [Mathur P, 2020]. In India, the systematic collection of data on cancer through the PBCRs and Hospital-Based Cancer Registries is in existence since 1981 under the National

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Cancer Registry Programme (NCRP), National Centre for Disease Informatics and Research (NCDIR) of the Indian Council of Medical Research (ICMR-NCDIR), Bengaluru [Sathishkumar K, 2022].

**2.1 Indian scenario:**

The incidence of PCa has steadily increased over the last ten years in Asian nations, particularly in Singapore, China, Malaysia, and Japan. This increase may be the result of dietary and other lifestyle changes. Because of the lack of PBCRs, careless case reporting, the stigma associated with PCa, and the paucity of community-based studies on the disease, the actual incidence of PCa in India is still unknown. According to Jain et al., 51,979 cases were anticipated in India in 2020 **(Gupta A**, 2020). The Indian Council of Medical Research's National Cancer Registry Program-National Center for Disease Informatics and Research (NCDIR: https://ncdirindia.org/All_Reports/Report_2020/default.aspx last accessed on February 21, 2023) report states that, between 2012 and 2016, the Delhi-National Capital Region had the highest age-adjusted incidence rate of PCa, with over 11.8 cases/million adults registered. Kamrup, Assam, came in second with ten cases/million adults, while Thiruvananthapuram had nine cases/million adults. Lifestyle-related variables and the lack of data collecting and reporting of cases in rural regions are the main causes of the statewide differences in PCa incidence rates in India (**Mathur P**, 2020).

The 2009–2011 National Cancer Registry Program reports from 25 population-based cancer registries (PBCRs) across India, including Bangalore, Barshi rural and expanded, Chennai, Delhi, Mumbai, Ahmedabad rural and urban, Aurangabad, Nagpur, Pune, Wardha, Kolkata, Kollam, Thiruvananthpuram, and North-East (Cachar District, Aizawl District, Dibrugarh District, Manipur State, Mizoram State, Imphal West District, Sikkim State, Meghalaya and Tripura State, Nagaland, Nagaland) were used to calculate the relative burden of prostate cancer in various Indian cities, as well as their corresponding Age Adjusted Rate (CR) and Age Adjusted Rate (AAR) per 100,000 populations (Anon., 2013). Prostate cancer is the third most common cancer site in males in India, after lung and mouth cancer [Sung H, 2021]. The age-adjusted incidence rate of prostate cancer varies from 11.8 per 100,000 persons in Delhi to 1.2 per 100,000 persons in West Arunachal Pradesh. The incidence is higher in urban and predominantly urban registries (>40% Urban), while many Northeastern registries reported lower incidence rates. The proportion of urban coverage in the registries has a positive correlation (0.65) with the incidence of prostate cancer. Research in China has also observed this urban pattern of prostate cancer [Roberts RO, 2004]. Some potential factors include increased rural-to-urban migration, altered dietary and lifestyle choices, more knowledge, and improved access to metropolitan medical facilities. Additionally, it's probable that not enough events from rural places are being reported [Yoo S, 2014].

The incidence of prostate cancer has been on the rise over time, with a notable APC of 2.6%. A pooled average of data from five registries between 1982 and 2016 produced this figure. 6.3 per 100,000 in Mumbai, 5.8 per 100,000 in Delhi, 5.1 per 100,000 in Bangalore, 2.5 per 100,000 in Chennai, and 2.2 per 100,000 in Bhopal were the incidence rates of prostate cancer in 1988. Several registries have also indicated an increase in cases of prostate cancer, according to previous research [Vickman RE, 2020]. Decadal differences in the ranking of prostate cancer between 1990–1996 and 2012–2016 also support the rise in incidence rates in both rural and urban registries [Lalitha K, 2012]. The APC was very high in Chennai (APC 4.4%), but it was not notable in the Bhopal register (APC 0.8%). The percentage change in the senior population component may be one reason for this discrepancy [Rastrelli G, 2013]. For instance, the proportion of Chennai residents aged 50 and beyond increased by 5.6% from 13.7% in the 1991 census to 19.3% in the 2011 census. By comparison, Bhopal's share increased from 10.8% to 13.9%, a 3.1% increase [Wilson RL, 2022]. Prostate cancer screening practices have been shown to be lower in Central India, indicating the need for further research into possible underreporting or missed detection in this area [Morgentaler A, 2009].

Similarly, the number of people under 50 has significantly increased, despite the fact that the frequency is increasing among the elderly. Prostate cancer was identified early (before the age of 60) in registries with a higher incidence rate. Further research is necessary to determine if this is the result of PSA-based screening, early exposure to risk factors, or genetic variables [Bhargavi R, 2023].

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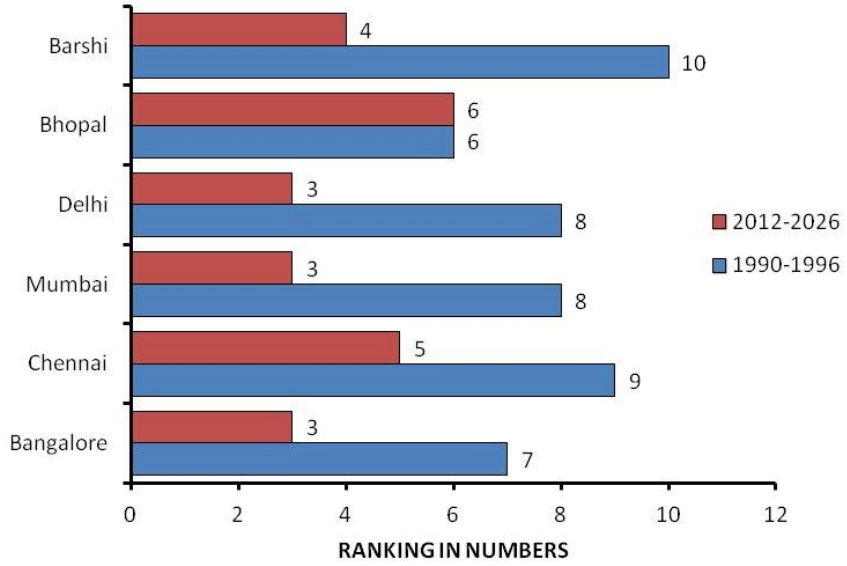


**Figure:** Histogram showing the rank status of the Cities among India predominant with Prostate cancer cases. Diagram redrawn from the data (Bhargavi R, 2023).

**2. Diagnosis:**

With about 400,000 fatalities per year, prostate cancer (PCa) is currently the second most frequent malignancy worldwide [Siegel, R.L.; 2023]. Due to the interplay of multiple risk factors, such as age, ethnicity, family history, lifestyle, environmental variables, and genetic factors, PCa develops in a complex manner. The basic cause of PCa is still not fully known despite continuous research efforts. Due to multiple studies showing that PSA serum levels frequently result in overdiagnosis and overtreatment, as well as the inability to reliably distinguish between low-, intermediate-, and high-risk PCa, screening for PCa using digital rectal examination (DRE) and serum prostate-specific antigen (PSA) has recently come under heavy fire [Siegel, R.L.; 2023].

Currently, transrectal ultrasonography (TRUS) guided needle biopsy of the prostate is the invasive method used to diagnose PCa [Guo, J.; 2020]. This approach has been connected to a number of negative outcomes. Furthermore, it was discovered that almost two-thirds of the biopsies performed after identifying elevated PSA levels were unnecessary, underscoring the marker's poor accuracy. As a result, PCa may be overdiagnosed and treated needlessly. Additionally, several studies have found that pathologists disagree about the Gleason scale, suggesting that using AI algorithms in computational pathology could be advantageous in providing extra assistance and a secondary assessment to medical professionals [Marron-Esquivel, J.M, 2023].

For males who present with suspected prostate cancer, multiparametric magnetic resonance imaging (MRI) of the prostate has been suggested as a first diagnostic test. A positive MRI result allows for MRI-directed sampling of lesions, while a negative MRI allows for the safe avoidance of biopsy [Barrett, T., 2023]. Prostate MRI's primary function is to identify only PCa that is clinically meaningful. About 30% of males who are referred to urology clinics have clinically severe PCa [Barrett, T., 2023]. This implies that invasive biopsy procedures may be performed needlessly on a significant number of patients. Up to half of these individuals, however, can safely forego the biopsy if an MRI scan yields a negative result.

Conversely, a positive MRI can reliably sample tissue and precisely target malignant lesions [Boehm, B.E.; 2023].

3.1 Different types of diagnosis methods available to detect PCa are:

**3.1.1 Digital rectal exam (DRE)**:

Individuals aged 45 and older are generally advised to undergo an annual digital rectal examination (DRE) as a stand-alone screening test for prostate cancer (PCa). There is no screening trial that has demonstrated DRE diagnostic performance in men as young as 45. One method for identifying prostate cancer is a digital rectal exam (DRE). A physician or nurse uses the rectum to feel the prostate. In order to check for lumps, hard spots, or enlargements that might be signs of prostate cancer, the patient lies on their side on an examination table with their knees drawn up to their chest. A blood test for prostate-specific antigen (PSA) is more effective than a DRE. Additionally, DRE's sensitivity and specificity are limited. DRE has a significant false-positive rate, according to several research (Krilaviciute A, 2023).

**3.1.2 Prostate-specific antigen (PSA) test**:

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Any screening test's main goal is to identify a pathological condition in its early stages so that prompt intervention may be made and needless morbidity or mortality can be avoided before clinical signs or symptoms appear. Since most men with early prostate cancer are asymptomatic, the most frequent initial laboratory finding in prostate cancer screening is an elevated serum PSA level. Given that the serum marker is elevated in both benign and malignant diseases, PSA is a very sensitive but somewhat general and imprecise screening tool (Gunes S., 2016). The columnar epithelium of prostatic tissue produces PSA, a serine protease enzyme. According to the US Preventive Services Task Force (2018), pro-PSA is the proenzymatic intracellular form of PSA. In the prostatic ducts, pro-PSA undergoes conversion to active PSA after passing through the basal and endothelial cell layers. It then penetrates the capillary membranes to enter the systemic circulation (Toktas G, 2013). When this active PSA reaches the bloodstream and stays unbound, a tiny percentage of it gets proteolyzed, turning it into free PSA. When circulating PSA enters the bloodstream, it quickly attaches itself to protease inhibitors (Taha DE, 2020). Since the free PSA/total PSA ratio tends to decline with malignancy, the age-adjusted percent free to protein-bound PSA ratio is a helpful indication of cancer.

By chemically dissolving the proteins semenogelin and fibronectin, which give normal semen its initial gel-like consistency, PSA reduces seminal viscosity. This decreased viscosity facilitates sperm migration into the cervix and increases fertility in general. The generation of spermatozoa changes as men age, which has a negative impact on the quantity and quality of sperm and hinders reproductive function (Leal J, 2018). Additionally, PSA levels rise with age, which is thought to be an evolutionary adaptation that increases fecundity over competing males and confers genetic fitness. The requirement for age-specific normal ranges for blood PSA levels and the rising incidence of diseases like benign prostatic hyperplasia in the general population may both be partially explained by this adaptation. Instead of producing more PSA than benign cells, prostate cancer cells typically produce less. Malignant cells, on the other hand, make it easier for PSA to enter the extracellular fluid around them and eventually enter the bloodstream. This process happens as a result of the cancerous prostate cells' absence of the basal layer, which would normally prevent PSA from passing through the cell. PSA may not be produced by highly undifferentiated cancer cells with a very high Gleason score (Klotz L. 2013).

**3.1.3 Transrectal ultrasound (TRUS)**:

Depending on how aggressive the tumor is, prostate cancer can be classified as low-, intermediate-, or high-risk. The way prostate cancer manifests itself has changed significantly since the 1970s. Prior to the widespread availability of transrectal ultrasound (TRUS) and PSA testing, the majority of patients had cancer-specific symptoms due to locally advanced disease, and DRE was used to detect the tumors; as a result, most patients were diagnosed at stage T2 or higher. With over half of all newly diagnosed patients falling into the "favourable risk" group, the majority of cases (>90%) are now diagnosed at an asymptomatic early stage (stage T1) because to the widespread use of PSA testing and TRUS-guided biopsies.

Transrectal ultrasonography, or TRUS for short, is a technique that creates an image of the pelvic organs. It is most frequently used to evaluate the prostate gland with an ultrasound-guided needle biopsy in men who have high prostate-specific antigen or prostatic nodules on a digital rectal exam. Prostate cancer, benign prostatic hyperplasia, or prostatitis may be discovered via TRUS-guided biopsy. TRUS can be used to stage primary rectal cancer and may also be used to identify other lower rectum disorders (O' Donoghue PM, 2010). The preferred method for imaging the prostate is still TRUS. However, greyscale ultrasound has a 50–60% accuracy rate and a 6% positive predictive value for prostate cancer detection, despite technological advancements in high-frequency wideband probes. Additionally, its local staging accuracy is rather low (Harvey CJ, 2012). However, due to the wide range of ultrasound appearances, the low specificity of sonographic abnormalities, the fact that tumors are often multifocal, and the high percentage of isoechoic cancers that cannot be distinguished from benign changes, TRUS is limited in its ability to detect prostate cancer (Raja J, 2006).

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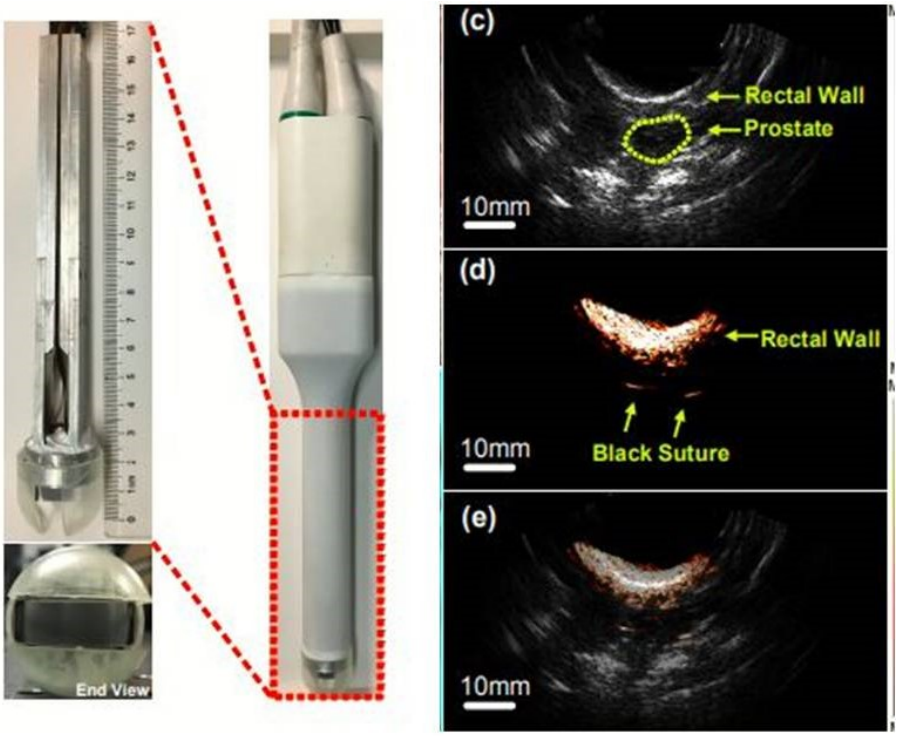


**Figure:** Image of the transrectal photoacoustic probe real photo. **Right:** The ultrasound images (Image retrieved from Liu, Chengbo et al, 2019).

**3.1.4 Magnetic resonance imaging (MRI)**:
The use of magnetic resonance imaging (MRI) in the treatment of prostate cancer has grown. Since functional MRI sequences were developed, MRI has already become a crucial tool for identification and staging. It is being investigated whether recent developments in artificial intelligence and radiomics can enhance detection, evaluate aggression, and serve as a valuable prognostic indicator (Glazer DI, 2015). MRI can help with pretreatment risk assessment, which in turn helps with patient selection and active surveillance follow-up. Targeted biopsy, therapy planning, and post-treatment follow-up to evaluate local recurrence can all be guided by MRI. Emerging technologies such as whole-body MRI and combined positron emission tomography/MRI have made MRI more significant in the assessment of metastatic disease, enabling improved detection and quantification (Fernandes MC, 2022).

Magnetic resonance imaging (MRI) is more effective than the other modalities at identifying the index primary prostatic lesion. Prostate cancer is now frequently detected, staged, and treated using the multiparametric MRI (mpMRI) procedure. This is especially true given technological advancements. A convincing example is the PROMIS trial on prostate magnetic resonance imaging (MRI), which found that mpMRI had a much greater sensitivity for detecting clinically relevant cancer 93% of the time compared to MRI and 48% of the time compared to transrectal US-guided biopsy (Fernandes MC, 2022). In order to improve sensitivity and specificity, MpMRI procedures for prostate cancer detection and diagnosis combine functional sequences of DWI and DCE-MRI with anatomical sequences of T1-weighted images (T1WI) and multiplanar T2-weighted images (T2WI). The anatomical detail of the prostate can be vividly portrayed by MRI, with greater soft tissue resolution T1WI for prostate versus periprostatic fat) and zonal anatomy (T2WI imaging for identifying peripheral, transition, and central zones) (Woo S, 2018).

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7.2 MRI-targeted biopsy: Over the past few decades, MRI has been able to increase prostate cancer detection, which has expanded its use beyond staging to include diagnosis. A "paradigm shift" from TRUS-guided biopsy to MRI-targeted or guided biopsy (MRI-Tb) was also brought about by this. The excellent negative predictive value (89%) of MRI for the diagnosis of csPCa serves as justification for its use in targeted biopsy (Seetharam Bhat KR, 2021). Furthermore, MRI-stratified pathways, either by using MRI-Tb alone or in conjunction with systematic US-guided biopsies, detect more clinically significant Prostate cancer (csPC) with a relative diagnosis rate of 1.45 compared with transrectal US-guided biopsy, according to randomized controlled trials, such as the PRECISION trial (Kasivisvanathan V,, 2018). According to the PROMIS experiment, because mpMRI has a strong negative predictive value (89% for mpMRI and 74% for TRUS), over 25% of men could avoid prostate biopsy if it were used as a triage test (Ahmed HU, 2017). Prostate MRI is sometimes used to assess additional prostate issues, such as infection (prostatitis) or prostate abscess, benign prostatic hyperplasia (BPH), an enlarged prostate, birth defects, and other difficulties following pelvic surgery.

**3.1.5 Prostate biopsy**:

A prostate biopsy involves taking tiny, hollow needle-core samples from a man's prostate gland in order to check for prostate cancer. It is usually carried out when a PSA blood test yields a high result (Ilic D, 2018). Additionally, if a digital rectal exam (DRE) reveals a potential abnormality, it can be deemed prudent. PSA screening is debatable because it can rise as a result of infections, non-cancerous disorders such benign prostatic hyperplasia (BPH), or prostate manipulation after surgery or catheterization. Furthermore, a lot of prostate tumors found by screening progress so slowly that they wouldn't cause issues for a man in his lifetime, negating the need for treatment-related consequences. Urine containing blood is the procedure's most common side effect (31%). Infection (0.9%) and mortality (0.2%) are possible additional adverse effects (Bell N, 2014).

**3.1.5.1 Ultrasound-guided prostate biopsy**

Through the urethra, the perineum, or transrectally, the procedure can be carried out. Transrectally is the most popular method, and tactile finger guidance was used in the past. The most prevalent method of prostate biopsy as of 2014 was transrectal ultrasound-guided prostate (TRUS) biopsy (Roberts MJ, 2017). Extended biopsy plans remove 12 to 14 cores from the prostate gland in a methodical manner from various prostate locations using a tiny needle (Patel AR, 2009). Through the urethra, the perineum, or transrectally, the procedure can be carried out. Transrectally is the most popular method, and tactile finger guidance was used in the past. The most prevalent method of prostate biopsy as of 2014 was transrectal ultrasound-guided prostate (TRUS) biopsy (Roberts MJ, 2017). Extended biopsy plans remove 12 to 14 cores from the prostate gland in a methodical manner from various prostate locations using a tiny needle (Patel AR, 2009).

**3.1.5.2 MRI-guided targeted biopsy**

Because prostate cancer cannot be seen on ultrasonography due to low soft tissue resolution, TRUS biopsy has been used to diagnose the disease in an almost blind manner since the mid-1980s. However, since around 2005, multi-parametric magnetic resonance imaging (mpMRI) has been utilized to more accurately detect and describe prostate cancer (Bonekamp D, 2011). When T2-weighted, dynamic contrast enhanced, and diffusion-weighted imaging were combined, a study comparing MRI and surgical pathology specimens showed a sensitivity of 59% and specificity of 84% in detecting cancer (Isebaert S, 2010). MRI-guided targeted biopsy can identify many prostate tumors that traditional biopsy is unable to detect (Marks L, 2013). Indeed, a prospective, investigator-blinded study comparing TRUS and MRI-guided targeted biopsy showed that MRI-guided biopsy reduced the diagnosis of insignificant or low-risk disease by 89.4% and enhanced the detection of significant prostate cancer by 17.7% (Pokorny MR, 2014).

Prostate biopsies can be performed in two ways employing MRI guidance, or "targeted" biopsy:

1. **Direct "in-bore"** is also termed as biopsy inside the MRI tube. MRI imaging is used to guide a needle into the prostate to take tissue samples during a direct "in-bore" biopsy of the prostate. It's a sophisticated and accurate way to identify prostate cancer. Direct MRI-guided in-bore prostate biopsy offers a precise and adaptable method for precisely sampling worrisome lesions, enhancing the diagnosis of clinically relevant malignancies. This is made possible by the direct visualization of the needle, needle guide, and needle trajectory (Debora Z. Recchimuzzi, MD, 2024).

2. **Fusion biopsy** using a system that combines stored MRI with real-time ultrasound (MRI-US) (Moore CM, 2013). A fusion prostate biopsy is a technique that combines MRI and ultrasound imaging of the prostate to collect samples. It makes it simpler to find lesions mentioned in the MRI by providing 3-D images of the prostate. A needle is used to take prostate samples from the designated locations (Marks L, 2013).

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**3.1.6 Positron emission tomography (PET) scan**:

One imaging technique that can identify prostate cancer is a positron emission tomography (PET) scan using prostate-specific membrane antigen (PSMA). It is thought to be the most effective way to visualize prostate cancer (Kwon DH, 2022). One of the most prevalent cancers in men is prostate cancer. Prostate cancer detection and treatment will be much enhanced by the novel prostate-specific membrane antigen (PSMA) PET imaging. For the purpose of imaging PSMA-positive lesions in men with prostate cancer using positron emission tomography (PET), the FDA approved the medication. A radioactive imaging agent called 68Ga-PSMA-11 attaches itself to prostate cancer cells and aids in their localization.

PET scan is further sub-classified into $^{18}$F-NaF PET/CT, choline-based PET/CT, fluciclovine PET/CT and PSMA-targeted PET/CT.

1. **$^{18}$F-NaF PET/CT:** One particular potential agent for PET/CT imaging of tumor cell proliferation, especially in prostate cancer, is 18F-fluorocholine. Because it eliminates distant metastases and assesses the response to hormone therapy, it is a useful tool in the early diagnosis of marrow-based metastases. Furthermore, as degenerative alterations are not choline-avid, 18F-fluorocholine may be able to distinguish between malignant and degenerative osseous abnormalities. However, the agent may accumulate in recent traumatic bone lesions. Conversely, 18F-NaF PET/CT is typically used to evaluate response to treatment, assess primary and secondary osseous cancers, and clarify abnormalities on other imaging modalities or clinical data. It can also show accelerated bone turnover. Although 18F-NaF PET/CT is a very sensitive technique for assessing bone metastases from prostate cancer, its specificity is difficult due to tracer build up in inflammatory and degenerative bone disorders (Beheshti M, 2016).

2. **Choline-based PET/CT:** One kind of imaging test that uses a radioactive version of choline to help detect prostate cancer is called a choline PET/CT scan. It can assist medical professionals in locating prostate cancer and determining whether it has returned. For the assessment of prostate cancer, whole-body positron emission tomography/computed tomography (PET/CT) using (11) C- and (18) F-labeled choline derivatives has become a viable molecular imaging technique. When the serum prostate-specific antigen level is greater than 1.0ng/mL, individuals with biochemical recurrence of the illness following definitive therapy can benefit from the successful restaging of prostate cancer using (11)C- and (18)F-choline PET/CT. Because of their poor spatial resolution, (11)C- and (18)F-choline PET/CT are less useful for the early staging of prostate cancer and for identifying small lymph node metastases. All things considered, patients who have a high pre-test suspicion of metastatic disease benefit most from these modalities (Kitajima K, 2013).

3. **Fluciclovine PET/CT:**

A nuclear medicine imaging test called a fluciclovine PET/CT scan uses computed tomography (CT) and positron emission tomography (PET) to identify prostate cancer. In patients with increased levels of prostate-specific antigen (PSA), it is used to identify recurrent prostate cancer (Rais-Bahrami, S., 2021). Early and accurate identification of recurrent lesions is essential for treatment, especially when they are tiny and most responsive to salvage therapy (Giovacchini G,, 2010). A popular molecular imaging technique for locating recurring lesions in individuals with prostate cancer is Positron Emission Tomography (PET). In certain kinds of prostate tumors or in patients with lower PSA recurrence levels, older PET radiopharmaceuticals such fluorodeoxyglucose and choline perform poorly (Jadvar H, 2013). Prostate specific membrane antigen (PSMA)-targeting compounds and $^{18}$Fluorine ($^{18}$F)-fluciclovine are examples of next-generation radiopharmaceuticals that exhibit promising outcomes. The Food and Drug Administration (FDA) and European Commission have approved $^{18}$F-Fluciclovine, a synthetic amino acid radiopharmaceutical, for the diagnosis of prostate cancer in individuals with high PSA after previous therapy (Jadvar H, 2013).

4. **PSMA-targeted PET/CT:**

Glutamate carboxypeptidase II (GCP II), another name for prostate-specific membrane antigen (PSMA), is a transmembrane glycoprotein that is significantly produced in prostate cancer cells.1, 2 On a variety of substrates, the glycoprotein functions as a glutamate carboxypeptidase, and its enzymatic activity enables the synthesis of certain inhibitors that are internalized following ligand interaction (Maurer T, 2016).

PSMA expression is believed to be elevated with the onset of androgen independence and tends to rise with greater pathological Gleason grade. PSMA-specific radiopharmaceuticals tagged with fluorine-18 ($^{18}$F) or gallium-68 ($^{68}$Ga) are both utilized in therapeutic settings. $^{18}$F has a half-life of 110 minutes and is created using a cyclotron, whereas 68Ga has a half-life of 68 minutes and is usually obtained using a generator (Meller BF, 2015).

18F-labeled PSMA-targeted radiopharmaceuticals can be produced and shipped off-site thanks to its prolonged half-life. Additionally, it is believed that these radiopharmaceuticals are linked to improved image resolution

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*Peer-Reviewed, Multidisciplinary & Multilingual Journal*
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(Chen Y, 2011). Today, $^{68}$Ga-PSMA-11, $^{18}$F-DCFPyL, and $^{18}$F-PSMA-1007 are the most commonly utilized PSMA-targeted PET radiopharmaceuticals in Canada. Anatomical localization and characterisation of PSMA-avid lesions are made possible by the use of hybrid PET/computed tomography (CT) or PET/MR scanners using PSMA-targeted radiopharmaceuticals (Haupt F, 2020).

**3.1.7 Risk stratification bioassay test**:
A blood or urine test used to assess prostate cancer risk is called a risk stratification bioassay test. These tests identify individuals with increased PSA levels who are unlikely to have clinically relevant cancer by using genetic or biochemical indicators (Lebastchi AH, 2020). In low-risk patients with moderately increased PSA values (<10 ng/mL), bioassay risk stratification testing may also aid in determining whether a prostatic biopsy is necessary. According to Parekh (2015), the main purpose of these blood or urine tests—My Prostate Score, the Prostate Health Index, 4K score, prostate cancer antigen 3, IsoPSA, SelectMDx, and EPI Exosome testing—is to identify individuals who have a low chance of developing serious cancer so they can safely forego biopsies.
If the test is negative, there is a great degree of confidence that the patient does not have clinically relevant prostate cancer because they have an excellent negative predictive value of >90% (Lebastchi AH, 2020). They play a crucial role in assisting in determining whether low- to medium-risk individuals and various borderline scenarios require a biopsy or even an MRI. Although their precise function is still unknown, they are also helpful for patients who are under active observation (Parekh DJ, 2015). The negative predictive value of bioassay risk stratification tests should be 90% or above. In low-risk people, a biopsy can be safely avoided if the test results are negative (Wei JT, 2023). In certain instances of PI-RADS 3 (borderline) findings on a prostatic MRI or a higher-risk patient with negative imaging who wants to forgo a biopsy, a risk stratification bioassay can also assist in reaching a final decision (Tosoian JJ, 2022). In these circumstances, it is vital to have a shared decision-making process with the patient. Only when the results will be utilized to inform clinical management decisions—typically to halt additional research and resume normal surveillance in the event of a negative test—should bioassay risk stratification testing be carried out. If a biopsy is done regardless of the result, bioassay testing is not required (Wei JT, 2023).

3.1.8 **Germline testing**:
A genetic test called germline testing for prostate cancer can be used to identify individuals or their family members who may be at higher risk of getting prostate cancer. For patients with metastatic, recurring, or high-risk prostate cancer, it is the accepted course of treatment (Russo J, 2022). The National Comprehensive Cancer Network and European guidelines for prostate cancer have made germline genetic testing a standard-of-care prescription for men with high-risk localized, metastatic, or recurring prostate cancer.1–4 Because of the quick decline in sequencing costs and the creation of sophisticated DNA and RNA sequencing methods to detect pathogenic variations, technological advancements have made it possible for this recommendation to be widely adopted (Cornford P, 2020).

There are two reasons why germline testing is advised. First, estimating the risk of developing a malignancy gives important information that can alert families to clinical symptoms of concern and, if necessary, result in early cancer screening and risk-reducing treatment for the patient and impacted family members. Second, with the development of precision medicine, some germline variations may have therapeutic implications for men with metastatic castration-resistant prostate cancer. PARP inhibitors may be used to treat men who have specific DNA repair abnormalities, such as BRCA1 or BRCA2, identified by germline or somatic sequencing.

For males who have been genetically chosen and have metastatic castration-resistant prostate cancer, rucaparib (Abida W ,2020) and olaparib (Hussain M, 2020) are both approved treatments. Furthermore, the existence of germline mutations as a biomarker of interest may be a prerequisite for enrollment in certain therapeutic trials. Lastly, uncommon patients with Lynch syndrome who might benefit from immune checkpoint inhibitor therapy can also be found via mismatch repair and microsatellite instability tumor testing.

Although there are still unanswered questions about how to efficiently and fairly conduct broad testing in this sizable group, germline testing has become the accepted standard for men with metastatic or high-risk prostate cancer. The expenses of testing and worries about the gathering and sharing of genetic data are potential hazards that could impact their capacity to secure life and disability insurance, however this might not be a major issue since the patients have already received a cancer diagnosis (Abida W, 2019).

Additionally, patients may be concerned about their privacy when disclosing their genetic information. Last but not least, some patients might not wish to be aware of their risk for developing further cancers, and unintentional findings of genetic alterations of questionable importance could cause further worries and concerns that would

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not have arisen otherwise. In light of these, during the course of their treatment, medical oncologists, urologists, or radiation oncologists frequently start the dialogue with men who have prostate cancer (Kwon DH, 2023).

**3.1.9 Single-cell RNA-sequencing (scRNA-seq)**:

According to Global Cancer Statistics 2022, among genitourinary malignancies in men worldwide, prostate cancer (PCa) has the highest age-standardized incidence rate (29.4%) and age-standardized mortality rate (7.3%) (Bray et al. 2024). Even with the impressive successes of androgen deprivation therapy (ADT) and surgical resection in early-stage PCa, postoperative recurrence and metastasis remain significant treatment hurdles (Simon et al. 2022). Relying exclusively on tumor cell research is insufficient for therapeutic therapy of PCa, which frequently has subtle early signs and a poor prognosis in advanced stages. According to Yu et al. (2023), PCa proliferation, invasion, and metastasis are significantly influenced by the functional alterations and spatial distribution features of cells in the tumor microenvironment (TME). The cellular heterogeneity of PCa is difficult to analyze and characterize using the traditional methods of bulk RNA sequencing and fluorescence-activated cell sorting. Detailed cellular transcriptional profiles can be created by using single-cell RNA sequencing (scRNA-seq) technology, which can record the RNA expression profiles of individual cells. When used in conjunction with Gene Ontology (GO), cell trajectory, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, scRNA-seq predicted signaling pathways, clarified cell differentiation or development processes, and offered new insights into cell function (Zhang et al. 2021). However, when cells were isolated, the original tissue's spatial character was lost. By obtaining the cell's RNA information for in situ sequencing, spatial transcriptome sequencing (ST-seq) gets around this restriction (Zheng, Fang 2022). Understanding the molecular pathways of carcinogenesis, invasion, metastasis, treatment resistance, and immune escape is possible through the use of scRNA-seq and ST-seq technologies in PCa research (Jin et al. 2021). With advantages such cell type and gene identification, correlation with clinical symptoms, and insights into tumor heterogeneity, evolution, and ecosystem, single-cell RNA sequencing (scRNA-seq) has greatly revolutionized PCa research in recent years (Gao T, 2022).

## CONCLUSION

Prostate cancer diagnostic technologies have advanced significantly in recent years to increase the precision of prostate cancer detection and prevent overdiagnosis and overtreatment. Nevertheless, elevated serum PSA levels and/or digital rectal examinations (DREs) still raise the possibility of prostate cancer. When prostate cancer is limited to the prostate, it is regarded as localized and perhaps treatable. A digital rectal examination (DRE), a blood test for prostate-specific antigen (PSA), and a biopsy are among the procedures used to identify prostate cancer. The most popular technique for identifying prostate cancer is a TRUS-guided biopsy. In summary, magnetic resonance imaging (MRI) is a non-invasive method that can be used to identify, describe, and stage prostate cancer. Prostate cancer biopsies are becoming more accurate thanks to new technologies.

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