



## Early Detection of Prostate Cancer

Worldwide, Prostate Cancer is common and is one of the main causes of cancer-related death in the male population. At the same time, in many cases, prostate cancer grows so slowly that it does not impact survival; hence, routine screening for early detection is controversial. Without screening, many cases of prostate cancer do not ever become clinically evident. Data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced. The use of PSA in the screening, detection and prognosis of prostate cancer has revolutionized the diagnosis and treatment of this disorder with an increase in detection rates and organ-confined[prostate cancer[1]. Despite these benefits and ease of implementation, tracking Prostate Cancer remains a matter of great controversy.

The incidence of prostate cancer has been increasing worldwide in recent years. The GLOBOCAN project showed that prostate cancer was the second most frequently diagnosed cancer and the fifth leading cause of cancer mortality among men worldwide in 2012.

This trend has been growing even in Asian countries, where the incidence had previously been low. However, the accuracy of data about incidence and mortality due to prostate cancer in some Asian countries is limited. The cause of this increasing trend is multifactorial. One possible explanation is changes in lifestyles due to more Westernized diets. The incidence is also statistically biased by the wide implementation of early detection systems and the accuracy of national cancer registration systems, which are still immature in most Asian countries.<sup>1</sup>

PCa is the most prevalent male malignancy in many regions of the world. However, remarkable racial and ethnic differences in the incidence have been reported, ranging from 4.4 per 100 000 to 118.2 per 100 000 persons in India and the USA, respectively. Additionally, it represents the second most common cause of cancer related mortality in the USA and Europe.<sup>2-3</sup>

Mortality rate decreases in Australia, New Zealand and Japan since the 1990s are possibly due to the improvements in treatment and/or early detection efforts employed. However, this rate is increasing in the majority of other Asian countries.

Studies of latent and incidental prostate cancer provide less biased information. The prevalence of latent and incidental prostate cancer in contemporary Japan and Korea is similar to those in Western countries, suggesting the influence of lifestyle changes on carcinogenesis.<sup>4</sup> Many studies reported evidence of both congenital and acquired risk factors for carcinogenesis of prostate cancer. Recent changes in the acquired risk factors might be associated with the increasing occurrence of prostate cancer in Asian countries. This trend could continue, especially in developing Asian countries.

Researchers at the University of Birmingham are developing a new type of test that uses complex sugars to detect prostate cancer earlier and with greater accuracy. The test works by identifying sugars, known as glycans, in blood. These sugars are attached to protein molecules called PSA and are known to undergo distinct but subtle changes when cancer is present in the body.

Particular types of glycans are associated with different cancers – but until now, there has been no technology available to detect the glycans in an accurate, timely and sufficiently specific way.<sup>5</sup>

A referral to a cancer genetics professional is recommended if there is a known or suspected cancer susceptibility gene. *BRCA1/2* pathogenic mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. Consequently, it is reasonable for men with germline *BRCA1/2* mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather

than every other year. Medications such as 5 $\alpha$ -reductase inhibitors (finasteride and dutasteride) are known to decrease PSA by approximately 50%. PSA values in these men should be corrected accordingly.<sup>6</sup>

The best evidence supports the use of serum PSA for the early detection of prostate cancer. DRE should not be used as a stand-alone test. DRE may be strongly considered as a baseline test in addition to serum PSA in all patients as it may identify high-grade cancers associated with “normal” serum PSA values. Consider referral for biopsy if DRE is suspicious for cancer.

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Medications such as 5 $\alpha$ -reductase inhibitors (finasteride and dutasteride) are known to decrease PSA by approximately 50%. PSA values in these men should be corrected accordingly. Testing after 75 years of age should be done only in very healthy men with little or no comorbidity (especially if they have never undergone PSA testing or have a rising PSA) to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread testing in this

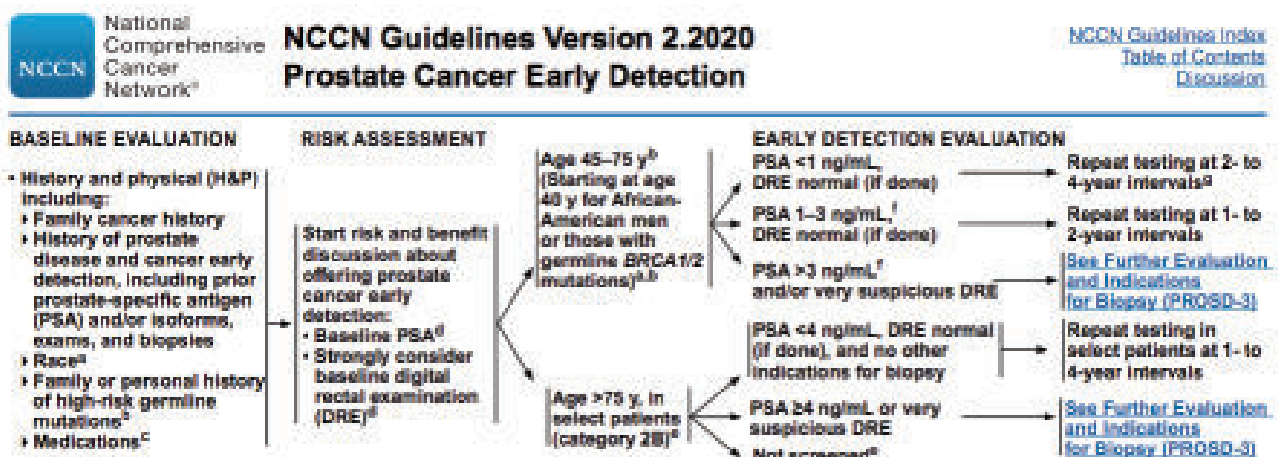
population would substantially increase rates of over-detection and is not recommended.<sup>8-10</sup>

The median PSA values for men aged 40–49 years range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher the median, the greater the risk. Men  $\leq$ 60 years with PSA <1.0 ng/mL and men >75 years of age with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases. This low risk is especially true for those in the latter category.<sup>11</sup>

The use of prostatic specific antigen (PSA) for screening, detection and prognosis of prostate cancer (PCa) greatly impacted the diagnosis and treatment of this disease. An increase in detection rate was observed, particularly a tremendous growth in the detection of organ-confined disease. North America has a high incidence of Prostate Cancer but low mortality.<sup>12</sup>

Recently, a Spanish study, where the incidence and mortality are similar to the USA, showed no benefit of screening on mortality, justifying the theory that locals with low mortality do not benefit from screening.<sup>11</sup> In Sweden and Denmark, with the same mortality rates as Brazil, screening lowered the rate more recently.<sup>7,8</sup>

Although with clear benefits and is easy to perform, Prostate Cancer screening is very controversial. In the northern hemisphere countries, where screening protocols were applied to populations at risk, it was observed an initial reduction of morbidity and mortality rates was followed by stagnation of these rates. This epidemiologic kinetics, although with a low



level of evidence, lead the American Urological Society not to recommend the use of vast screening of risk groups in North America.<sup>13</sup> Prostate cancer is one of the most common cancers affecting men; however, deciding whether to be screened is complex and personal. Screening to detect and treat prostate cancer in men without symptoms may offer benefits but is also associated with harm.

Prostate cancer screening has the potential to help find prostate cancer early, when treatment can be more effective, ultimately saving lives. Still, there are also significant harms of screening that people should be aware of. One of the most important harms of screening is frequent false-positive results, which often lead to additional testing and years of follow-up, including repeated blood tests and biopsies. Another important harm is overdiagnosis, which happens when screening leads to the diagnosis of prostate cancer in some men who would not have experienced symptoms from cancer during their lifetime. Thus, the treatment of these men provides them with no benefit and can lead to harmful outcomes. Common harms associated with treatment include erectile dysfunction and urinary incontinence. Finally, the benefits of screening are often realized years after treatment, while the harms may occur soon after testing or treatment and may last for some time.

Our current recommendation is that men aged 55 to 69 should decide whether to be screened after a conversation with their doctor about the potential benefits and harms. For men aged 70 years and older, the potential benefits do not outweigh the harms, and these men should not be routinely screened for prostate cancer.

For example, when a man aged 55 to 69 years is interested in the small potential benefit and more willing to accept the potential harms, screening may be the right choice for him. On the other hand, a man who places more value on avoiding potential harm may choose not to be screened. We encourage primary care clinicians to be aware of the USPSTF recommendations in regards to prostate cancer screening and encourage these clinicians to continue to have these conversations over the years, as each patient's values and situation may change.

The Task Force aims to keep all recommendations current, updating each recommendation approximately every 5 years, though the timeline may vary. Given the importance of prostate cancer

screening, we anticipate it will likely follow our standard approach.<sup>14</sup> The U.S. Preventive Services Task Force recommends that physicians screen men aged 55 to 69 years for prostate cancer on a patient-to-patient basis and that those older than 70 years should not be screened. The American Academy of Family Physicians does not recommend routine screening in men aged 55 years and older. In comparison, the American Cancer Society recommends screening at age 40 based on a man's life expectancy and risk – and only after he has been advised of the “uncertainties, risks and potential benefits” of screening. The American Cancer Society (ACS) recommends that men have a chance to make an informed decision with their healthcare provider about whether to be screened for prostate cancer. After getting information about the uncertainties, risks, and potential benefits of prostate cancer screening, the decision should be made. **Men should not be screened unless they have received this information.** The discussion about screening should take place at:

**Age 50 for men at average risk** of prostate cancer and are expected to live at least 10 more years. **Age 45 for men at high risk** of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father or brother) diagnosed with prostate cancer at an early age (younger than age 65). **Age 40 for men at even higher risk** (those with more than one first-degree relative who had prostate cancer at an early age).<sup>15</sup>

After this discussion, men who want to be screened should get the prostate-specific antigen (PSA) blood test. The digital rectal exam (DRE) may also be done as a part of screening. If, after this discussion, a man cannot decide if testing is right for him, the screening decision can be made by the health care provider, who should consider the man's general health preferences and values. If no prostate cancer is found as a result of screening, the time between future screenings depends on the results of the PSA blood test:

- Men who choose to be tested and who have a PSA of less than 2.5 ng/mL may only need to be retested every 2 years.
- Screening should be done yearly for men whose PSA level is 2.5 ng/mL or higher.

Because prostate cancer often grows slowly, men without symptoms of prostate cancer who do not have a 10-year life expectancy should not be offered testing

since they are not likely to benefit. Overall health status, and not age alone, is important when making decisions about screening. Even after a decision about testing has been made, the discussion about the pros and cons of testing should be repeated as new information about the benefits and risks of testing becomes available. Further discussions are also needed to consider changes in a man's health, values, and preferences.

#### Upcoming alternative screening and follow-up test

It is generally agreed that the prostate-specific antigen (PSA) blood test is not perfect for finding prostate cancer early. It misses some cancers, and it sometimes finds cancers that never need to be treated. Researchers are working on strategies to address these issues. The new tests are based on other forms of PSA and other tumour markers. Several more unique tests seem to be more accurate than the PSA test, including:

- The **Prostate Health Index (PHI)**, combines the results of total PSA, free PSA, and proPSA to help determine how likely it is that a man has prostate cancer that might need treatment
- The **4Kscore test**, which combines the results of total PSA, free PSA, intact PSA, and human kallikrein 2 (hK2), along with some other factors, to help determine how likely a man is to have prostate cancer that might need treatment
- Tests (such as **ProgenSA**) look at the level of **prostate cancer antigen 3 (PCA3)** in the urine after a digital rectal exam (DRE). The DRE pushes some of the prostate cells into the urine. The higher the level, the more likely that prostate cancer is present.
- Tests that look for an abnormal gene change called **TMPRSS2:ERG** in prostate cells in urine collected after a DRE. This gene change is found in some prostate cancers but rarely in the cells of men without prostate cancer.
- **ExoDx Prostate(IntelliScore)**, or **EPI**, is a test that looks at levels of 3 biomarkers in a urine sample to help determine a man's risk of having aggressive (high-grade) prostate cancer.
- **Confirm MDx** is a test that looks at certain genes in the cells from a prostate biopsy sample.

These tests aren't likely to replace the PSA test any time soon, but they might be helpful in certain situations. For example, some of these tests might be useful in men with a slightly elevated PSA to help

determine whether they should have a prostate biopsy. Some of these tests might be more helpful in determining if men who have already had a prostate biopsy that didn't find cancer should have another biopsy. Some newer lab tests (known as **genomic or proteomic tests**) can be used along with other information (such as the PSA level and grade of cancer) to help better predict how quickly a prostate cancer might grow or spread. These tests examine which genes (or proteins) are active in prostate cancer cells. Examples of such tests include:

- **Oncotype DX Prostate:** This test measures the activity of certain genes in prostate cancer cells and reports it as a score on a scale from 0 to 100 (higher scores indicate cancer that is more likely to grow and spread quickly, as well as a higher risk of dying from prostate cancer).
- **Prolaris:** This test measures the activity of a different set of genes in prostate cancer cells and reports it as a score on a scale from 0 to 10 (higher scores indicate cancer that is more likely to grow and spread quickly, as well as a higher risk of dying from prostate cancer).
- **ProMark:** This test measures the activity of a set of proteins in prostate cancer cells and reports it as a score that helps predict how likely a cancer is to grow and spread quickly.
- **Decipher:** For men who choose surgery to treat their cancer, this test can help determine the risk that cancer will come back in other parts of the body after surgery (and, therefore, if these men should consider further treatment). This test measures the activity of certain genes in prostate cancer cells from the surgery specimen.

These new blood-based test for prostate cancer has a significant potential to reduce the number of biopsies needed, resulting in reduced healthcare costs and improved patient care.<sup>16</sup>

Considering the ease of spread through asymptomatic carriers of SARS-CoV-2, minimizing patient and healthcare provider exposure is crucial for patient and occupational safety. To minimize exposure, it is paramount to practice social distancing (at least six feet apart) in order to minimize contact between individuals and the health care system. Furthermore, much like in non-pandemic times, the NCCN endorses the principles of shared-decision making, recognizing the unique needs of every patient.<sup>17, 20</sup>

Finally, the NCCN recommends that healthcare providers follow guidance from local governments and leadership within individual healthcare systems. From a surgical perspective, in mid-March, the American College of Surgeons and Surgeon General recommended that health systems, hospitals, and surgeons attempt to minimize, postpone, or outright cancel electively scheduled operations. Subsequently, the American College of Surgeons provided further guidance on the triage of non-emergent surgeries, including an aggregate assessment of the risk incurred from surgical delays of six to eight weeks or more as compared to the risk of proceeding with the operation. As during non-pandemic times, principles of shared decision-making when it comes to PSA testing for prostate cancer should continue, with the goal of recognizing and meeting the unique needs of each patient.<sup>18-20</sup>

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