Diagnosis of prostate cancer: the implications and proper utilization of PSA and its variants; indications and use of MRI and biomarkers

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Prostate cancer screening remains highly controversial in medicine. The College of Family Physicians of Canada currently endorses positions that recommend against prostate-specific antigen (PSA) screening in men of all ages, while the Canadian Urological Association recommends shared and informed decision making for PSA screening in men 50-70 years old. Unfortunately, these opposing stances have left Family Physicians responsible for interpreting the appropriate course of action for their patients. Recent studies demonstrating an increase in incidence of metastatic prostate cancer have led to our support of the Canadian Urological Association recommendations.

In an attempt to facilitate initial patient investigation, this article aims to outline current prostate cancer screening recommendations, as well as the various screening modalities available. The utility of PSA-based tests, serum and non-serum biomarkers, and multiparametric magnetic resonance imaging is discussed and evaluated.

Key Words: biomarkers, prostate cancer screening, recommendations

Prostate cancer screening

The goal of prostate cancer screening is the early detection of clinically significant prostate cancer as opposed to low-risk disease that would otherwise have no clinical impact. Despite all the advances in screening technology, prostate cancer screening remains one of the most controversial topics in urology. In a Cochrane review published in 2013, systematic prostate-specific antigen (PSA) screening resulted in higher diagnoses of prostate cancer but yielded no benefits for overall survival (OS; RR: 1.00; 95% CI, 0.96-1.03) or cancer-specific survival (CSS; RR: 1.00; 95% CI, 0.86-1.17).[1,2]

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Moreover, screening-associated overdiagnosis and overtreatment, with consequences such as decreased patient quality of life and economic burden on the system, have led to guidelines discouraging the use of systematic PSA screening in Europe and the United States.[3] However, based on the conclusions of three randomized control trials (the Prostate, Lung, Colon, and Ovarian screening trial (PLCO),[4] the European Randomized Study of Screen for Prostate Cancer (ERSPC; 21% RR reduction in prostate cancer mortality),[5] and the Goteborg randomized trial of PSA screening (42% RR reduction in prostate cancer mortality),[6] the Canadian Urological Association (CUA) concluded that PSA screening appears to reduce prostate cancer mortality, supporting their suggestion to have a discussion about screening in men between the ages of 50-70 who were interested in

pursuing examinations.[7] Despite the recommendation to offer PSA screening, the CUA recognizes the risk of overdiagnosis and overtreatment, especially since up to 67% of men diagnosed with prostate cancer will be identified as having clinically insignificant disease (no impact on morbidity or mortality).[7] Therefore, there is a large emphasis on the importance of detailed investigation prior to proceeding with prostate biopsy. Investigations including PSA measurements and its variants, emerging serum and non-serum biomarkers, and new prostate imaging techniques will help guide clinical decision-making, with the aim to reduce unnecessary prostate biopsies.

Informed decision-making

It is necessary to hold a thorough discussion regarding the pursuit of prostate cancer screening with patients meeting screening recommendation criteria as per CUA recommendations highlighted below.[7] It is essential to outline both the benefits and risks associated with prostate cancer screening while taking into account the personal values and interests of the patient. Important risks of prostate cancer screening include potential harm from prostate biopsy (e.g. bleeding, infection or sepsis) and psychological stress endured by the diagnosis of prostate cancer, specifically in cases where men may not have clinically significant disease. Consequently, the CUA stresses that prostate screening is to remain an individualized process. Informed men between the ages of 50-70 requesting prostate cancer screening should be given a digital rectum examination (DRE) and PSA testing.

The College of Family Physicians of Canada and CUA stances on prostate cancer screening

In 2012, the United States Preventative Services Task Force (USPSTF), a panel that did not include urologists or cancer specialists, recommended against PSA screening on the basis that the small decrease in mortality provided by screening does not outweigh the harms of screening and overdiagnosis.[8] Following suit in 2014, the Canadian Task Force on Preventative Health Care (CTFPHC) published a strong recommendation against PSA screening in men less than 55 years of age, and men greater than 70 years of age. In addition, they recommended against PSA screening for men between the ages of 55-69 years.[9] Subsequently, the College of Family Physicians of Canada (CFPC) endorsed the statements of the CTFPHC. This opinion opposed statements made by both the CUA,[7] the American Society of Clinical Oncology (ASCO),[10] and other societies,[3,11] which recommended shared decision making for PSA screening in men aged 50-70 and 55-69, respectively. Unfortunately, this has left Family Physicians hesitant because of two contradictory positions on PSA screening without clear direction.

Following the recommendations of the USPSTF against PSA screening, studies were employed to determine long term outcomes. In the 2 years following USPSTF recommendations, there was a significant decrease in PSA screening tests administered and biopsy volume decreased by 31%. It was also reported that patients were more likely to be diagnosed with high-risk disease/metastatic disease and less likely to be diagnosed with intermediate-risk/curable disease.[12] It is important to note that these conclusions were drawn from registry-based studies, which may have overemphasized the potential downside of the recommendation against use of PSA testing without considerations for the pitfalls such as overtreatment. Nonetheless, analysis of the USPSTF recommendations found major flaws in the trials on which the recommendations were based. In depth analysis revealed a high rate of non-protocol PSA measurements in the control group, which may have rendered the results of the trial inconclusive. In addition, authors found that the trials had a median follow up of approximately 10 years, which was believed to be inadequate for slowly progressing prostate cancer. Some of the other studies used when performed in pure – unscreened or contaminated populations, show increased survival and a smaller number of patients needed to screen to cure one individual.[13] Furthermore, an epidemiological study in 2018 found that the incidence of metastatic prostate cancer in the United States was increasing by 2.74%/yr in 2012 following the statements of the USPSTF, compared to a previous decline in metastatic prostate cancer incidence by 1.45%/yr in 2007.[14] Another imperative aspect to consider was that one of the major rationales behind the recommendations of the USPSTF and the CTFPHC was the overtreatment of low-risk prostate cancer and its associated morbidity. In 2009, conservative management was utilized in 6.7% of cases of low-risk prostate cancer in the United States. Between 2010 and 2013, conservative management for men with low-risk PCa, rose sharply to 40.4% of cases [15]. An increased uptake of active surveillance as a treatment modality demonstrated that urologists are being more responsible with low-risk and intermediate-risk patients; thus, more responsible with PSA screening results. This, as well as a concerning trend of increased high-risk disease at presentation, has led to our strong support of CUA guidelines on PSA screening.

PSA screening recommendations, Figure 1

For men electing to undergo PSA screening, the CUA recommends that PSA measurements begin at age 50 for most men, and at age 45 for men with an increased risk of developing prostate cancer.[7] Primary risk factors for prostate cancer that influence PSA screening practices include age (> 50 yr) and family history of prostate cancer. In men aged < 50 years, history of prostate cancer in a first-degree or second degree relative conferred a five-fold and two-fold risk of receiving a prostate cancer diagnosis, respectively, and therefore screening can be offered at 45 years.[16] Men with African ethnicity origin show higher incidences of prostate cancer and generally have a more lethal course of disease and therefore can be offered screening at 45 years.[17] Interestingly, the risk of developing metastatic prostate cancer within 15 years in men less than 45 years was very low, including men who tested in top PSA percentiles. Therefore, PSA screening for men under 45 is unlikely to provide any benefit.[16]

Since 2017, the CUA guidelines suggest that the interval between PSA testing should be based upon initial PSA measurements. For men with PSA < 1 ng/mL, PSA testing should be repeated every 4 years, as the risk of developing metastatic disease within 15 years for a man of any age with a PSA < 1 ng/mL is very low.[7] Baseline PSA levels above 1 ng/mL are at increased risk of clinically significant prostate cancer and/or prostate cancer metastasis several decades later[18,19] and therefore the CUA recommends offering repeat PSA screening every 2 years. For PSA levels > 3 ng/mL, the CUA have not specified an optimal testing interval, but recommend more frequent PSA testing and further investigations with adjunctive testing strategies (PSA velocity, PSA density and percent free PSA).

As per CUA recommendations, screening discontinuation should be based on current PSA levels and life expectancy. For asymptomatic men at age 60 with PSA level < 1 ng/mL, the risk of developing metastatic prostate cancer is low and therefore standard screening is no longer justified.[7] Similarly, the CUA recommends discontinuing PSA screening in asymptomatic men at age 70 as the ERSPC trial concluded that screening at > 70 yr did not reduce prostate cancer mortality,[5] though PSA testing can be continued in those who are interested. In addition, the CUA recommends discontinuing PSA screening in men with a life expectancy less than 10 years. For men with a high risk of mortality from external factors, PSA screening is unlikely to provide any benefit and therefore should not be offered or can be discontinued.[20] Ultimately, the health care provider should take into account the patient's current age, general health status, and values/interests when deciding to offer PSA screening.

PSA investigations

Most prostate cancers are located in the peripheral zone of the prostate and pathologies may be detected by DRE when volume > 0.2 mL. Serum PSA is an organ-specific but not cancer-specific serum marker, and therefore can be elevated in non-malignant prostate pathologies such as benign prostatic hyperplasia (BPH), and prostatitis. Moreover, men may present with prostate cancer despite having low serum PSA.[21] Clinically, prostate cancer is suspected on the basis of abnormal DRE and/or elevated PSA levels. In asymptomatic men with total serum PSA levels between 2-10 ng/mL, further risk investigation including prostate volume assessment to calculate PSA density, PSA kinetics, and free/total PSA ratio are recommended prior to proceeding with prostate biopsy.[3] Initial prostate investigations begin with serum PSA levels, its variants, and the DRE and should be used in accordance to guide clinical decision-making.

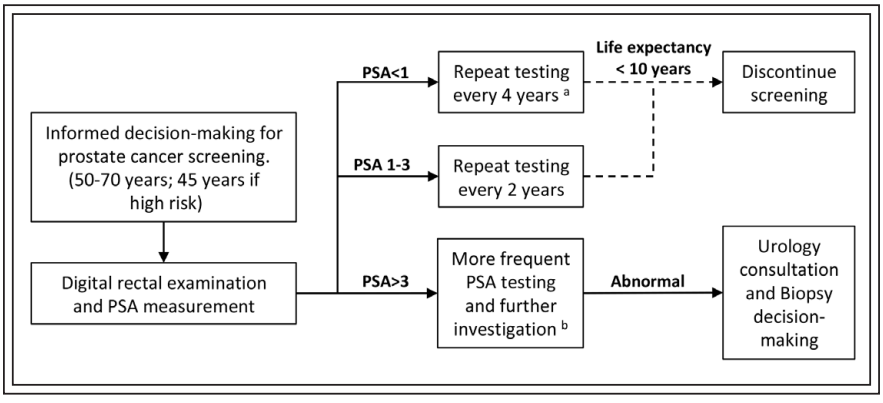

Figure 1. Prostate cancer screening decision-making algorithm. **a)** Discontinue screening in asymptomatic men if age > 60 and PSA < 1 ng/mL. **b)** e.g., Free/total PSA, serum and non-serum biomarker tests, etc. PSA = prostate-specific antigen.

PSA density

PSA density (PSAD) is the serum PSA divided by transrectal ultrasound (TRUS)-determined prostate volume. Prostate volume can also be assessed by transabdominal ultrasound, CT imaging or MRI. Some studies have shown that a PSAD threshold of < 0.15 ng/mL/cm^3 in a highly selected population with limited cancer on biopsy distinguished men with insignificant tumors,[22] whereas other studies failed to validate these findings.[7] The CUA therefore discourages the use of PSAD alone but instead suggests that it should be used as an adjuvant to absolute PSA levels in order to contribute to clinical decision-making.

PSA kinetics

PSA velocity (PSAV), the absolute annual increase in serum PSA (ng/mL/year), and PSA doubling time (PSADT) are both measures of how serum PSA is changing over time. Indeed, substantial increases in PSA over time is concerning and warrants further investigations. Some studies have shown that a PSAV greater than 0.75 ng/mL/year indicate increased risk of prostate cancer, and that PSAV may potentially be used as a prognostic tool for prostate cancer treatment, while other studies have shown conflicting evidence.[7] Additionally, PSA kinetics are limited as a diagnostic tool due to variations in PSA measurement intervals. As such, the CUA discourages the use of PSA kinetics alone; it should be used to provide additional information about prostate cancer risk.

Free/total PSA ratio

The ratio of free to total PSA is useful for men with a total PSA of 4-10 ng/mL and a negative DRE. Studies preceding the use of biomarkers and MRI to determine prostate cancer risk (discussed below) demonstrated that prostate cancer was detected by biopsy in 56% of men with a free-to-total ratio less than 0.1 ng/mL, but in only 8% of men with a free-to-total ratio greater than 0.25 ng/mL.[23] In other words, a higher free-to-total ratio was found to confer a lower risk of harboring prostate cancer. It is important to note that the free-to-total PSA ratio has no clinical use if serum PSA is > 10 ng/mL or during follow up for known prostate cancer.[3] Similar to serum PSA levels, the free/total PSA ratio can fluctuate, thus repeated testing is necessary before clinical decision-making. As such, the CUA does not recommend using the free/total PSA ratio alone for clinical decision-making, but it is an effective tool for men with elevated serum PSA levels in determining if prostate biopsy is necessary.

Prostate cancer related biomarkers

In order to avoid unnecessary biopsies, the European Association of Urology (EAU) recommend that all asymptomatic men with PSA between 2-10 ng/mL receive further risk assessment in addition to PSA measurements and its variants. Further investigation includes either a validated prostate cancer risk calculator, or additional biomarker testing (4Kscore, PHI test, or PCA3 test).[3] The CUA recognizes that in men with moderately elevated PSA (2-10 ng/mL), biomarker tests such as the 4Kscore, PHI, PCA3, SelectMDx, and ExoDx are emerging as very effective tools in predicting clinically significant prostate cancer when compared to PSA measurements alone. At the current moment, many of these tests are not publicly funded in Canada,[7] nonetheless, their use is increasing in the urology community due to their effectiveness and potential to reduce unnecessary prostate biopsies from occurring.

Serum liquid Testing; 4Kscore

Aside from direct PSA related measurements, additional biomarkers measured in patients' blood serum may be used to estimate prostate cancer risk. The four-kallikrein panel (4Kscore) is a test that measures free, total, and intact PSA and human kallikrein-like peptidase 2. The test combines these results with age, DRE results, and prior biopsy status to estimate patient risk of harboring "clinically significant " cancer meaning Gleason 7 or greater disease.[7] Although popular since it was one of the first biomarker tests available, the 4Kscore relies heavily on PSA parameters, presenting a large problem for the select population of men harboring clinically significant disease without elevated PSA levels.[21] Additionally, the Centers for Medicare and Medicaid Services (USA) will not cover 4Kscore testing under Medicaid as they found an absence of clinical utility and had significant issues with validating initial findings,[24] therefore this test is not recommended.

Serum liquid testing; Prostate Health Index (PHI)

PHI is a validated test that measures free and total PSA, and the (-2)pro-PSA isoform to similarly estimate the risk of harboring Gleason 7 or greater disease. The PHI test is a commercially available test that outperformed free/total PSA in distinguishing clinically significant disease, specifically in men with PSA between 2-10 ng/mL.[25] The PHI and 4Kscore tests both performed similarly in predicting high-risk prostate cancer in men in a direct comparison between the two.[26] Since the clinical effectiveness of the 4Kscore was not validated during further investigations, the PHI test should also be used with caution.

Serum liquid testing; NK Vue

Natural killer (NK) cells are involved in tumor cell immunosurveillance and decreased NK cell activity (NKA) has been associated with prostate cancer. The NK Vue test involves an in vitro assay using 1 mL of the patient's blood. In a small pilot study, NKA was measured prior to prostate biopsy using the NK Vue blood test. The study concluded a positive predictive value of 86% and a negative predictive value of 69% using a cut off of 200 pg/mL for NKA and that low NKA values were more likely to be associated with a positive prostate biopsy.[27] NK Vue is an emerging, commercially available test that is relatively inexpensive and may provide helpful information in predicting high-grade prostate cancer.

Non-serum liquid testing: Prostate Cancer Antigen 3 (PCA3)

PCA3 is a prostate-specific non-coding mRNA biomarker that can be measured in urine following prostatic massage during DRE. Progensa, the commercially available PCA3 test, was found to be superior to total and free/total PSA for the detection of prostate cancer in men with elevated PSA.[28,29] The indication for PCA3 testing is in men with a previous negative biopsy result to determine if a repeat biopsy is necessary. A large prospective study demonstrated that men with a history of negative prostate biopsy who scored lower than 25 on the Progensa test were approximately 5 times less likely to have a positive repeat biopsy when compared to men who scored 25 or greater.[30] The PCA3 test has not been validated for biopsy-naïve patients i.e. patients being treated with active surveillance.

SelectMDx

SelectMDx utilizes clinical findings (PSAD, DRE, PSA, age, history of biopsy, and family history of prostate cancer) and RNA levels of *HOXC6* and *DLX1* genes measured in post-DRE urine, to predict Gleason ≥ 7 disease on biopsy. Unlike the 4Kscore, SelectMDx relies less on PSA findings and incorporates unrelated RNA profiles to assess prostate cancer risk, not limiting its effectiveness in the select men harboring clinically significant disease that present with normal PSA profiles. In a prospective study of 519 patients scheduled for biopsy, the SelectMDx algorithm achieved an AUC of 0.90 (95% CI, 0.85-0.95) for the detection of high-grade prostate cancer.[31] The study concluded that the algorithm resulted in better prostate cancer risk stratification when compared to current clinical practices. Overall, Select MDx is a promising algorithm that incorporates clinical findings and biomarkers to predict high-grade prostate cancer, an additional tool that could reduce the number of unnecessary prostate biopsies.

ExoDx Prostate Intelliscore (EPI)

EPI combines clinical findings (age, PSA, race, family history of prostate cancer) with expression of PCA3 and ERG found within patients' urine to predict Gleason ≥ 7 disease on biopsy. One advantage of the EPI test is that it does not require post-DRE urine, which may benefit patients undergoing testing.[32] The test was validated in 1064 patients scheduled for biopsy (≥ 50 years, prostate cancer free, PSA 2-20 ng/mL).[33] When compared with clinical findings alone, the addition of the PCA3 and ERG biomarkers in the EPI test was associated with improved discrimination between Gleason 7 or greater and Gleason 6 and benign disease (AUC = 0.73, 95% CI: 0.68-0.77 in EPI versus AUC = 0.63, 95% CI: 0.58-0.68 in clinical findings alone). The authors also concluded that if the EPI test had determined biopsy decisions in their study, 27% of biopsies (138 out of 519) would have been avoided, missing only 5% of patients with Gleason 7 (4+3) disease. EPI is another promising test available that may reduce the number of unnecessary prostate biopsies by better discriminating clinically significant disease.

Serum (4Kscore, PHI) and non-serum (PCA3, SelectMDx, EPI) biomarkers for prostate cancer detection have become a popular tool in distinguishing between clinically significant and non-significant disease. In addition to the patients' clinical presentation and findings, these biomarker tests are more effective than PSA measurements alone in predicting high-grade disease. These available tools can be used to help guide clinical decision-making, potentially reducing the number of unnecessary biopsies performed, Figure 2.

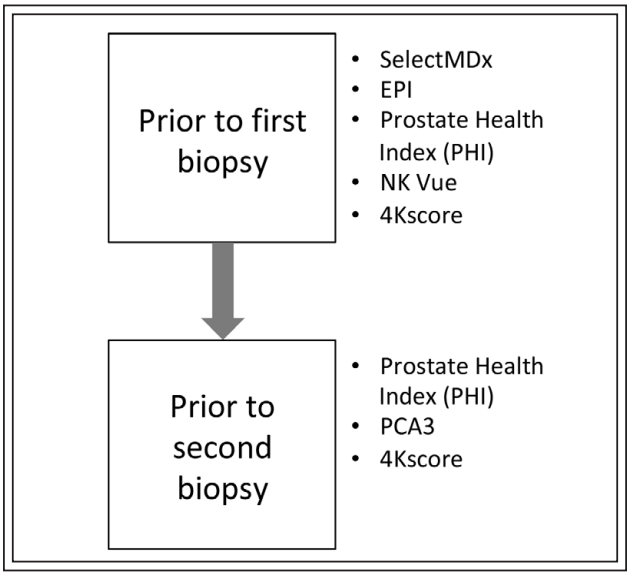

Figure 2. Prostate cancer biomarker tests and the decision points in which they have been validated.

Prostate risk calculators

The use of nomograms to assess the risk of clinically significant prostate cancer before biopsy are attractive as they are easy to use, available online and supplement the use of PSA alone.[7] Among the most widely used calculators, the PCPT[34] and ERSPC[35] prostate cancer risk calculators are the most popular. These and similar calculators can be used to assess the risk of harboring clinically significant prostate cancer prior to biopsy, though a systematic review and meta-analysis demonstrated that only few of the available calculators improved the predictive accuracy of PSA testing to detect clinically significant prostate cancer (among the few were the PCPT and ERSPC risk calculators).[31]

Multiparametric magnetic resonance imaging (mpMRI) of the prostate gland

mpMRI combines anatomical and functional MR sequences to investigate any lesions in the prostate. The combination of sequences (dynamic contrast enhancement, T2W-weighted imaging and diffusion weighted imaging) allows for the interpretation of any suspicious lesions and may help guide prostate biopsy.[36] Dynamic contrast-enhanced images utilize IV contrast to assess the vascularity of the prostate. Prostate cancer tumors can be localized due to increased blood flow on imaging because of neovascularization that often accompanies the tumor's growth. T2W-weighted imaging reflects local tissue water and may be used to delineate the anatomy of the prostate i.e. the peripheral and transition zone. Diffusion weighted imaging analyzes the motion of water molecules. Due to the relatively increased density of tissue found in cancer tissue, there is less motion detected on imaging. This can help localize prostate cancer lesions. These sequences can combine digitally to generate a 3D representation of the lesion's location. Subsequently, the image can be used to help guide prostate biopsy. If there is an abnormal finding, ultrasound of the prostate is digitally mapped with the MRI image in real time using a fusion software, allowing the operator to target specific abnormal areas during the biopsy procedure. The CUA does not recommend mpMRI followed by targeted biopsy in biopsy-naïve men with an increased risk of prostate cancer (elevated PSA/risk calculator), as Cancer Care Ontario released a systematic review indicating that the diagnostic abilities of mpMRI were poor to moderate in a biopsy-naïve setting.[37] Thus, systematic TRUS-guided biopsy (with no prior imaging) remains the gold standard for biopsy-naïve men. However, in men with a prior negative TRUS-guided biopsy who show signs of increased prostate cancer risk (increasing PSA levels or increasing abnormalities in DRE), mpMRI followed by targeted biopsy, may prove helpful in diagnosing more clinically significant prostate cancer, and fewer low-risk cancers when compared to patients with a repeat TRUS-guided biopsy.[7,38]

PIRADs scoring system

The reporting of prostate mpMRI examination is expressed using the Prostate Imaging – Reporting and Data System (PIRADS) score. Using parameters such as T2-weighted, diffusion weighted, and dynamic contrast enhanced imaging of the mpMRI, a sum is calculated from values assigned to each variable and is interpreted according to the PI-RADS classification which ranges from 1 to 5, with 1 being most probably benign and 5 most probably malignant.[39,40] In a phase II retrospective clinical trial, it was concluded that the global consensus PIRADS showed high sensitivity and positive predicted value, reduced surgery for indolent prostate cancer [41], and improved the diagnosis of clinically significant prostate cancer when compared to standard diagnostic tools such as transrectal ultrasound biopsies.

Prostate biopsy

Ultrasound-guided biopsy

In ultrasound-guided biopsy, the standard biopsy approach in the context of prostate cancer, the operator uses ultrasound during the procedure to guide their needle. The most common approach for prostate sampling is transrectal ultrasound-guided biopsy (TRUS), while a transperineal approach may be implemented for men who cannot undergo a transrectal procedure e.g. anal stenosis.[42] TRUS is performed in an office setting with local anesthesia. Both the ultrasound probe and biopsy needle are inserted through the rectum and the prostate is sampled extensively in a systematic, but blind fashion (the samples taken are "randomly"). Though some studies suggest that prostate volume should be taken into account when performing a biopsy,[43] a standard 12 core biopsy approach is often implemented, sampling from the apex, base, mid-prostate and lateral aspects of the prostate on each side. In addition to systematic sampling, specific guided sampling of abnormal areas (e.g. hypoechoic regions, DRE, MRI) may be carried out.

Gleason score and new ISUP

The Gleason score system is utilized by pathologists to grade prostate cancer. When analyzing a prostate biopsy, there is often variation in regard to the grade

TABLE 1. **Interpretation of ISUP grade groups**

ISUP grade group	Gleason score equivalent	Risk group
Grade group 1	Gleason score < 6	Low
Grade group 2	Gleason score 7 (3+4)	Intermediate favorable
Grade group 3	Gleason score 7 (4+3)	Intermediate unfavorable
Grade group 4	Gleason score 8	High
Grade group 5	Gleason score 9-10	High

of cancer present between different areas of a single sample. As such, two grades are assigned to the two areas that comprise the majority of the cancer within the sample, grade 1 having the best prognosis, grade 5 having worst. The two grades are added to yield the Gleason score. When reporting a Gleason score, the grade of the largest and most abnormal area of the sample is reported first. For example, a biopsy sample scored with Gleason 7 (4+3) refers to a lesion that is primarily comprised of grade 4 findings, while fewer areas of the lesion are grade 3.[44,45]

In 2015, the International Society of Urological Pathologists (ISUP) released a revised and simplified prostate cancer grading system called the ISUP Grade Groups. There are 5 grades, 1 through 5. These grades groups are based on the traditional Gleason score and are associated with prostate cancer risk groups, Table 1.[46,47] Both scoring systems are used in practice.

Conclusion

As Family Physicians, individualized discussions regarding the pursuit of PSA screening should be held with all patients meeting CUA prostate cancer screening guidelines. Asymptomatic men with an abnormal DRE, and men with PSA > 3 ng/mL, as well as abnormal serum/non-serum biomarker test results should receive a referral to a specialist. In addition, symptomatic men showing signs of lower urinary tract symptoms (frequency, urgency, incontinence etc.) should also receive a referral to a specialist. Although it is recommended by national CUA guidelines for men 50-70 years old, PSA screening remains a controversial decision. While former kinetics and PSA-based calculations have helped in the guidance of patient counseling for prostate biopsy, the emergence of biomarkers (SelectMDx, etc.) and mpMRI continue to grow as more specific tools for accurate patient counseling prior to prostate biopsy. With the well-known overdiagnosis and overtreatment of Gleason 6 non-significant prostate cancer, these non-invasive tools are growing in the urological community to assist in improved patient care and counseling. We hope that this article will empower Family Physicians to properly utilize prostate cancer screening modalities; allowing for appropriate escalation of patients to specialists for further investigation and management. □

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