Prostate Cancer Screening, Diagnosis and Risk Stratification

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1. Prostate Cancer Screening

1.1 Introduction

- Prostate cancer (PCa) is the most commonly diagnosed cancer and second leading cause of cancer death in men in the US.
- Approximately 268,490 men are diagnosed (1 in 8), and 34,500 men will have prostate cancer-related mortality (2.4% of men) in 2022[1].
- Over 60% of new cases are diagnosed in men aged 65 years and older, and the mean age at diagnosis is 66 years.[2]
- While most patients are diagnosed with localized and low-risk prostate cancer, there has been an inverse stage migration in prostate cancer temporally associated with the Grade D recommendation from the U.S. Preventive Services Task Force Recommendation in 2012.
- In 2018, the U.S. Preventive Services Task Force Recommendation changed their recommendation to Grade C acknowledging the moderate uncertainty of prostate cancer screening regarding the benefits and harms with PSA-based screening. It also recommended shared decision-making for screening decisions[4].
- **Current guidelines from the AUA, National Cancer Comprehensive Network and the American Cancer Society endorse shared decision-making for prostate cancer screening**[5,6,7]

1.2 Screening

- **The goals of cancer screening are to detect potentially lethal cancer at an early stage to intervene with curative intention and lower the burden of overall treatment.**
- **Prostate-specific antigen (PSA)** represents the mainstay of prostate cancer screening.
  - PSA is a reproductive protein produced by the glandular tissue of the prostate that aids in seminal fluid liquification. Normally the serum concentration of PSA is low, but it can increase with infection, inflammation, trauma, and prostate cancer. Due to the association with prostate cancer, PSA can be used for screening men at risk.
  - **The pathophysiology of PSA elevation in prostate cancer is the disruption of the glandular architecture and loss of the basal cell layer, resulting in leaching of the PSA into the blood stream** (loss of the basal cell layer is the histologic hallmark of prostate cancer).
  - PSA is an imperfect screening tool as it can be elevated in benign conditions of the prostate. In fact, prostate cancer cells make less PSA than do normal prostate cells and up to 15% of prostate cancers are diagnosed in men with “low PSA” levels (<4.0ng/dl).
- PSA screening strategies have been tested in 2 large clinical trials with disparate results:
  - The **US-based Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial found no reduction in prostate cancer-specific mortality associated with screening after a median follow-up of 10 years**.[9] This finding was confirmed on an updated 17-year analysis.[10]
    - Unfortunately, the study was **confounded by pretrial PSA testing** in 40% of the study subjects and **contamination** (by PSA testing during the trial period) in 70% of the "unscreened" control cohort during the study, with an **overall estimated contamination rate of 90%**.[11]
    - Several recent studies have demonstrated a higher rate of contamination in the control arm in the PLCO study, adding uncertainty regarding the quality of the evidence and implications of this trial.[11]
  - The **European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a statistically significant relative reduction of 21% in prostate cancer mortality at 11 years with prostate cancer screening**[12] At 16 years of follow-up, the risk reduction remained stable at 20%, with an estimated number needed to screen of 570 and the number needed to diagnose of 18 in order to prevent 1 death from prostate cancer.[13]

- In the longest and largest independent sub-group of the trial (**Goteborg**), **prostate cancer mortality was reduced by 46% at 14 years**, and in a modeling study of the ERSPC trial, cancer deaths were reduced by 21%, with 5 cancers needed to be detected over the lifetime of the screened subjects to prevent 1 death from prostate cancer.[14,15]

- PSA screening rates are declining because of the controversy and uncertain benefit of widespread population-based PCa screening.[9,12]
  - The US Preventive Services Task Force recommended against prostate cancer screening (Grade D) in 2008 for men 75 years and older followed by all ages in 2012 on the grounds that the potential harms outweighed the benefits for prostate cancer screening.[16]
    - Due largely to the Grade D recommendation, PSA-based screening declined in the U.S. for all men following the 2008 recommendation with a further decline for men aged 50-74 following the 2012 recommendation[17]
    - Lower PSA-based screening for prostate cancer was associated with a 6.5% annual decrease in overall prostate cancer incidence[17]
    - Despite the lower overall incidence, decreased screening has been associated with higher incidence of more aggressive pathologic features and metastatic prostate cancer at diagnosis.[18,19] Furthermore, the rates of prostate biopsies also declined after the Grade D recommendation.[20,21,22,23,24,25,26]
  - **In 2018, the US Preventive Services Task Force changed the recommendations to Grade C for prostate cancer screening for men aged 55 to 69 years old and Grade D for all men 70 years old or older**. For the grade C recommendation in younger men, the US Preventive Services Task Force endorse **individualized shared decision-making** where patients review estimates of personalized benefits (improved survival) and harms (over-diagnosis and over-treatment) prior to electing screening. For this age group, the task force guidelines stated that screening decisions should also include risk factors such as family history, race/ethnicity, and patient values and preferences.[27]

- In 2013, the AUA released the following **best practice statement** for prostate-specific antigen (PSA) screening:
  - **PSA screening in men under age 40 years is not recommended.**
  - **Routine screening in men between ages 40 to 54 years at average risk is not recommended.**
  - **For men ages 55 to 69 years, the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, shared decision-making is recommended for men aged 55 to 69 years that are considering PSA screening and proceeding based on patients' values and preferences.**
  - To reduce the harms of screening, **a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening** As compared to annual screening, it is expected that screening intervals of two years preserve the majority of benefits and reduce overdiagnosis and false positives.
  - **Routine PSA screening is not recommended in men over age 70 or any man with less than a 10 to 15-year life expectancy.**
- The National Comprehensive Cancer Network (NCCN) **Prostate Cancer Early Detection** recognizes the current mixed evidence and controversies for screening. **The guidelines currently recommend starting screening at age 45 years old with repeat testing for an initial PSA > 1 ng/ml every 1 to 2 years and at every 2 to 4 years for an initial PSA < 1 ng/ml. The panelists uniformly recommend against PSA screening for patients with less than a 10-year life expectancy**
- High-risk populations should undergo prostate cancer screening differently than the above “routine” screening recommendations. Screening should start at age 40 in these populations:
  - Patients with a cancer family history of prostate (especially metastatic), ovarian, pancreatic and breast, colorectal or endometrial either at younger age or multiple relatives
  - **Black/African American men**
  - **Patients with a germline BRCA 2 or HOXB13 mutations and likely those with BRCA 1, ATM, mismatch repair (MLH1, MSH2, MSH6, PMS2)**

Table 1

Risk factor	Relative risk of prostate cancer
1st degree relative diagnosed <60 years	2.1-2.8
Above germline mutations	2-5.8
African ancestry	1.6

- Several studies have found the **initial PSA at younger age are associated with subsequent risk of developing clinically significant PCa**. The median values of PSA at ages 40 – 49 and 50 – 59 years old are 0.7 and 0.9 ng/ml, respectively. Multiple studies in multiple diverse populations have validated these medians, demonstrating that an initial PSA < 1 ng/ml at 40 – 49 or 50 – 59 years old was associated with a low-risk of incident prostate cancer. Additionally, increases above these levels are strongly associated with developing clinically aggressive or advanced PCa.[28-30]
- Data comparing the Goteborg cohort of the ERSPC trial to the Malmo natural history cohort identified that continued screening of men with a PSA <2.0 ng/ml does not result in differences in prostate cancer mortality, **whereas if the PSA at 60 is > 2.0ng/ml, the number needed to screen is 23 with only 6 requiring diagnosis to prevent 1 death at 15 years, suggesting a higher risk population for directed PSA screening**[31]

1.3 Multi-parametric MRI in Prostate Cancer Screening

- Multiparametric Magnetic Resonance Imaging (mpMRI) is an imaging tool that can be used at multiple points in the evaluation of men at risk for prostate cancer.
  - Please see **Uroradiology Core: MRI**
    - **Section 1: Technical Considerations**
    - **Section 4: MRI of the Prostate**
- **mpMRI** involves – at the minimum - the acquisition of **T1- and T2-weighted images, diffusion-weighted imagines (DWI), and dynamic contrast enhanced images (DCE)**.[32] From these sequences, lesions can be identified and scored using the PIRADS v2.1 system delineating level of suspicion for harboring clinically significant prostate cancer (Table).[33] Identified lesions may be contoured for targeted biopsy using software fusion platforms.[34]
- As a **pre-biopsy screening tool**, studies have investigated the differences in screening results between mpMRI and standard extended-sextant biopsy pathways, showing that mpMRI had higher sensitivity and was more effective in detecting clinically significant disease, whereas the systematic biopsy approach was more effective in detecting low-risk disease.[35]
  - In the PROMIS study, 576 men underwent a 1.5 Tesla mpMRI followed by both TRUS biopsy and a template mapping prostate biopsy. **For clinically significant cancer, mpMRI was more sensitive (93%; 95% CI 88-96%) and less specific (41%; 95% CI 36-46%).** The authors concluded that using mpMRI to triage men might allow 27% of patients to avoid a primary biopsy, resulting in a 5% reduction in the detection of clinically insignificant cancers. Using mpMRI findings to direct subsequent TRUS-biopsies would detect up to 18% more cases of clinically significant cancers.[36]
  - In the PRECISION study, 500 men without a history of a prostate biopsy and a clinical suspicion for prostate cancer were randomized to undergo mpMRI with targeted biopsy versus standard TRUS prostate biopsy. Clinically significant prostate cancer was detected in 38% of the mpMRI targeted biopsy group as compared to 26% of the TRUS biopsy group (p=0.005) and fewer men in the mpMRI targeted biopsy group received a diagnosis of clinically insignificant cancer.[37]
  - In the MRI-FIRST study, 275 men with prostate cancer underwent systematic biopsy and sampling of a hypoechoic lesions on TRUS, if present, by one operator and then MRI-targeted biopsy only by a second operator, each blinded to the other proceduralist's sampling. Clinically significant prostate cancer was found in 37% of patients, with 66% of cancers found by both techniques, 20% by MRI-targeted sampling only , and 14% by systematic sampling only. The findings suggested no difference between systematic biopsy and targeted biopsy in the detection of clinically significant prostate cancers.[38]
- **For men with MRI-visible lesions,** there is utility of including both MRI-targeted and systematic biopsies.[39] **The current AUA position on mpMRI in the screening and diagnosis of men at risk for prostate cancer recommends that both targeted and systematic biopsies be performed in men undergoing MRI-targeted sampling**.
  - In the TRIO study, 2103 men with MRI-visible lesions underwent MRI-targeted and systematic prostate biopsy. The combined biopsy approach led to 9.9% increased overall prostate cancer detection and 21.8% upgrading to a higher-grade group relative to either biopsy method alone.[40]
- **For men with no MRI-visible lesions (PIRADS <3), PSA density can be used for further risk stratification.** Performing a biopsy in men with PSA density of 0.15ng/ml/ml or greater can decrease missed clinically significant prostate cancer from 9% to 2.4%.[41]
- **For men with a prior negative biopsy with continued PSA rise, mpMRI should be considered.**[42] If mpMRI-visible lesions are present, a mpMRI-targeted biopsy may be performed. The associated risk of prostate cancer detection with a positive mpMRI result is 34-68%.[43]
- Based on these studies, **mpMRI has demonstrated optimized detection of clinically significant prostate cancer in men with a clinical suspicion for prostate cancer who are either biopsy-naïve or have had prior prostate biopsy negative for prostate cancer**.
  - To date, the systematic biopsy sampling schema has not been replaced by mpMRI targeted biopsy sampling in biopsy naïve men.[10]

Table 2: PIRADS v2.1 Scoring system

PIRADS Score	Risk of Clinically Significant Cancer
1	Very low (clinically significant cancer is highly unlikely to be present)
2	Low (clinically significant cancer is unlikely to be present)
3	Intermediate (the presence of clinically significant cancer is equivocal)
4	High (clinically significant cancer is likely to be present)
5	Very high (clinically significant cancer is highly likely to be present)

1.4 Biomarkers in Prostate Cancer Screening and Diagnosis

- While PSA is a biomarker used in the initial screening of men at risk for PCa, the ability of PSA to rule out PCa is limited (see **section 1.2**). Additional biomarkers have been explored to aid in the screening of men at risk for PCa with a goal of **ruling out the need for initial or repeat biopsy**.
- **The following tests may be used in addition to or instead of mpMRI to aid in the selection of men for prostate biopsy.**
  - **Urine-based:**
    - **ExoDx™**: a urine-based 3-gene exosome (ERG, PCA3, and SPDEF) expression assay validated for the **risk of clinically significant PCa in men without a prior biopsy. This assay does not require a** DRE/prostatic massage prior to sample collection.[44]
    - **miR:** a urine-based test interrogates small noncoding RNAs (sncRNA) isolated from urinary exosomes. This test was developed and validated to stratify patients with prostate cancer into risk categories.[45]
    - **MPS** (MyProstateScore, formerly Michigan Prostate Score (MiPS)): combination of serum PSA, post-DRE urine PCA3 and TMPRSS2:ERG validated to assess the **risk of incident PCa and clinically significant PCa**. In validation studies it was shown to improve upon the performance of PSA or PCA3 alone in detecting aggressive PCa.[46]
    - **PCA3**: a non-coding mRNA in post-DRE urine, may help **identify incident and clinically significant PCa, particularly in patients with a prior negative biopsy**.[47]
    - **SelectMDx**: a urine-based risk assessment that measures DLX1 and HOXC6 against KLK3 mRNA levels in post-DRE urine validated for the **risk of clinically significant PCa (≥3+4) in men without a prior biopsy**.[48,49]
  - **Blood-based**:
    - **4-kallikrein (4Kscore®) panel**: a blood-based validated risk assessment for **clinically significant PCa in men at risk for PCa**.[50]
    - **PHI**: blood-based risk assessment using PSA, percent free PSA, and [-2]proPSA to estimate the **risk of clinically significant PCa**.[51]
  - **Tissue-based**:
    - **ConfirmMDx** is an epigenetic test of the PCa-associated genes GSTP1, APC, and RASSF1. It is assessed on non-cancerous biopsy tissue and is validated to predict **the absence of PCa on subsequent biopsy** (rules out need for further biopsy).[52]
- The following tests may be used for **risk-stratifying patients with newly diagnosed PCa**:
  - **Tissue-based** genomic biomarkers have been validated as a measure of risk stratifying patients with newly diagnosed PCa; however, **the performance of these tests is limited by tumor multifocality and heterogeneity**.[53,54] Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. These tests may be used selectively when added risk stratification may alter clinical decision-making.[55]
    - **OncotypeDX Prostate**: a 17-gene expression panel validated to predict the **risk of adverse pathology at surgery and the risk of metastasis and death after treatment**. It can be used to inform the decision between active surveillance and definitive therapy.[56]
    - **Prolaris**: a 31-gene expression panel validated to predict the **risk of disease-specific mortality with conservative management and the risk of metastatic disease after treatment**. It can be used following biopsy to better determine whether a patient should receive active surveillance or definitive therapy.[57]
    - **ProMark**: an 8-protein proteomic assessment validated to assess the **risk of adverse pathology**. May be utilized for low or very low risk patients post biopsy to select active surveillance versus definitive therapy.[58]
    - **Decipher**: a 22-gene genomic classifier that is validated to predict the **risk of metastasis** to select patients who are better treated with definitive therapy.[59]

Table 3: Prostate Cancer Biomarker

Test	Patient Selection	Result	Key Test Characteristic	Clinical Use
Urine-Based				
ExoDx	Pre-biopsy	Risk of clinically significant PCa (csPCa) on biopsy	NPV = 91%	Rule out need for a biopsy
miR	Pre- and Post-biopsy	Risk of PCa and csPCa on biopsy	Specificity = 96% AUC = 0.98 – 0.99	PCa risk stratification
MPS	Pre-biopsy	Risk of csPCa on biopsy	NPV = 98%	Rule out csPCa on biopsy
PCA3	Negative prior biopsy	Risk of PCa on biopsy	NPV = 88%	Rule out need for a repeat biopsy
SelectMDx	Pre-biopsy	Risk of csPCa on biopsy	AUC = 0.90	Select patients for biopsy
Blood-Based				
PHI	Pre-biopsy	Risk of csPCa on biopsy	AUC = 0.71	Rule out need for a biopsy
4K Score	Pre-biopsy	Risk of csPCa on biopsy	AUC = 0.82	Rule out need for a biopsy
Tissue-Based				
ConfirmMDx	Negative biopsy tissue	Risk of csPCa on biopsy	NPV = 90%	Assess need for repeat biopsy
OncotypeDX	Post-biopsy	Risk of pT3 or Gleason 4	AUC = 0.72 (combined with clinical variables)	Identify patients for treatment vs. surveillance
Prolaris	Post-biopsy	PCa specific mortality, biochemical recurrence, metastasis, biochemical failure, biochemical recurrence	AUC = 0.77 (combined with clinical variables)	Identify patients for treatment vs. surveillance

Promark	Post-biopsy	Risk of pT3 or Gleason 4	AUC = 0.65 – 0.72; Sensitivity 90%	Identify patients for treatment vs. surveillance
Decipher	Post-biopsy	Risk of pT3, Gleason 4, or N+	AUC = 0.75 – 0.82	Identify patients for treatment vs. surveillance. Assess the need for androgen deprivation therapy in addition to radiation for intermediate risk disease

Abbreviations: csPCa – clinically significant prostate cancer; NPV – negative predictive value; AUC – area under curve.

2. Prostate Cancer Diagnosis

2.1 Biopsy

- To diagnose PCa, a pathologic specimen is required. This is usually obtained by a needle biopsy of the prostate (PBx).
- A minimum of **12-core systematic PBx is recommended to establish PCa diagnosis**. Apical and far lateral cores should be included in the biopsy template. Cores should be labeled by location as this information can determine location of disease and treatment planning. Individual jars should contain no more than 2 cores to prevent tangling of cores and improve tissue sampling.
  - **For obvious locally advanced or metastatic disease a six-core "sextant" biopsy can be employed.**
- **Positive biopsy rates with standard systematic TRUS biopsy should be ~40-45% for biopsy naïve patients with elevated PSA. Major deviation from this yield should prompt an investigation into biopsy technique.**
- A protocol or "check-list" approach to biopsy should be used to ensure quality and safety.

2.1.1 Type of Prostate Biopsy

- Currently**, transrectal PBx** with ultrasound guidance is the most common approach for PBx. The biopsy is performed by passing a spring-loaded biopsy needle through a mounted guide on a rectal ultrasound probe. The rectal wall is pierced when directing the biopsy needle into the adjacent prostate.
  - **Recommended steps**:
    - Preparatory antibiotics (enema optional)
    - Note: rectal preparation with povidone-iodine seems to reduce post prostate biopsy infection.[60]
    - Perform rectal examination to assess prostate for mass and ensure no rectal pathology is present.
    - Insert TRUS probe gently.
    - Brief ultrasound assessment of the prostate.
    - Perform periprostatic block with local anesthetic (see section 2.1.2).
    - Full ultrasound assessment of prostate including size measurement, presence of lesions (hyper or hypoechoic areas), and calcifications. Recording of images is recommended.
    - Obtain biopsies. Directed biopsies are usually performed first. Assess the quality of core samples.
    - Remove probe
  - Advantages: less procedural pain, less local anesthetic necessary, less equipment, shorter procedure, targets the posterior prostate well.
- **Transperineal** PBx is performed by passing needles through the perineum to sample the prostate. This approach has a **lower risk of serious infection but is associated with higher pain scores when performed under local anesthesia** This approach i gaining popularity in the United States due to reduced risk of sepsis. Transperineal biopsy can be performed via free hand method, with transperineal access systems or using stepper and/or brachytherapy grid. The cancer detection rates are not significantly different between the transrectal and transperineal prostate biopsy approaches.
- One randomized trial noted that the preprocedural antibiotics can be eliminated without an increase in the risk of sepsis or UTI.[61] Several TP prostate biopsy templates such as Brazell template, Ginsburg protocol template, and MUSIC TP template are utilized by urologists with comparable cancer[62] detection rates.
  - Two multi-centered clinical trials (NCT04815876 and NCT04843566) will randomize patients to transperineal vs. standard transrectal prostate biopsy to assess the comparative effectiveness for detection of clinically significant prostate cancer and biopsy-related complications (infection and sepsis). All men will have mpMRI-targeted approaches for both arms.
  - Recommended steps:
    - Preparatory enema
    - Perform rectal examination to assess prostate for mass and ensure no rectal pathology is present.
    - Insert TRUS probe gently.
    - Brief ultrasound assessment of the prostate.
    - Sterilize perineum.
    - Perform perineal block with local anesthetic (see **section 2.1.2**).
    - Full ultrasound assessment of prostate including size measurement, presence of lesions (hyper or hypoechoic areas), and calcifications. Recording of images is recommended.
    - Obtain biopsies. Directed biopsies are usually performed first. Assess the quality of core samples.
    - Remove probe
  - Advantages: fewer or no antibiotics necessary, lower infection risk, targets anterior prostate and apex well
  - Disadvantages: Increased pain scores, increased expenditure of urology practices, increased time spent performing biopsy.
- PBx targeted at MRI-detected lesions improves yield and grade assessment. There are various forms of MRI-targeted biopsy.

Current guidelines recommend performance of both targeted sampling and template biopsy in men with MRI targetable lesions (see **section 1.3**).

- **Cognitive fusion** – location of MRI lesions is assessed by the proceduralist, and biopsies are directed at the area of concern as triangulated on the ultrasound imaging.
- **Software-based fusion** – The prostate and MRI lesions are contoured by radiologists. The contoured images are overlaid on TRUS images and electromagnetic tracking of the biopsy probe allows for directed biopsy of the lesions.
- **In-bore MRI PBx** – lesion is biopsied with MRI guidance while in the MRI magnet ("bore").

- **"Saturation" biopsy** patterns including greater than 12 cores can improve the diagnostic ability of PBx and can be useful in **patients with a prior negative PBx and/or negative mpMRI**.
- Although rarely employed, a finger-guided biopsy of the prostate can be done. This might be used in situations when ultrasound guidance is not readily available, and an obvious prostate mass is present. However, fewer biopsies are generally performed and there is a significant risk of needlestick injury to the operator.

2.1.2 Anesthetic Considerations for Prostate Biopsy

- **All non-sedated prostate biopsies should be performed with the addition of local anesthetics** and a thorough understanding of the neuroanatomy of the pelvis can aid in appropriate anesthetic delivery.
  - The average pain score on a prostate biopsy is 3-4/10; but **up to 20% of patients report an unwillingness to undergo a repeat biopsy** – which has significant implications when considering the role of active surveillance in low-risk men.
  - **Additionally, prostate biopsies can be psychologically distressing. When appropriate, consideration for anxiolytic therapy should be given**.
    - We advocate for low dose benzodiazepine therapy, such as 5mg of Valium, administered 30 minutes prior to the biopsy (and after obtaining consent) to assist with anxiety in selected patients. Additionally, this can be beneficial as a muscle relaxant in reducing anorectal tone and improving tolerance of probe insertion when placing the transrectal probe.
- Important Neuroanatomic Considerations:
  - Anorectal region: innervation is determined relative to the dentate line.
    - Proximal to the dentate line the rectum is innervated by the pelvic plexus from S3-4 nerve roots.
      - Most sensation is related to rectal distension and is not relieved by introduction of local anesthetics.
    - Distal to the dentate line the rectum is innervated by branches of the pudendal nerve.
  - Prostate: innervation is through the inferior hypogastric and pelvic plexus (S2-4 nerve roots).[63]
    - These parasympathetic and sympathetic fibers originate from S2-4 and coalesce at the tips of the seminal vesicles and then continue along the posterolateral surface of the prostate.
  - Perineal Tissues: Innervation is via the perineal branches of the pudendal nerve.[64]
    - These nerves are adjacent to the levator ani fascia.
- Approaches to local anesthesia during a prostate biopsy:
  - Anorectal: topical lidocaine can be used to reduce rectal pain from probe insertion.
    - Benzodiazepines can also be effective in reduce anorectal tone to reduce discomfort from insertion.
  - Prostate:
    - Pelvic plexus block: infiltration local anesthetics at the tip of the seminal vesicles.
    - Prostatic nerve block: infiltration of local anesthetic where the seminal vesicle and prostate meet.
      - The "Mount Everest" sign is commonly used to describe the triangular fat pad that marks the appropriate location for this approach[65].
      - See **Figure 1**
    - Periapical triangle block: infiltration of local anesthetic at the apex of the prostate.
      - This triangle is demarcated by the levator muscles (laterally), sphincter (medially) and the prostate (proximally).
      - In our experience, this is an effective block for apical biopsies; but often requires puncture of the rectum below the dentate line when performed transrectally and therefore patients should be warned for the increased pain during performance of this block.
      - See **Figure 2**[64]
    - Superficial perineal nerve block: infiltration of local anesthetic 2cm from midline, superficial and deep to the levator ani fascia at the level of the posterior prostate[64].
- In our experience we recommend using 1% lidocaine with 5mL injected per site of anesthetic need. Bupivacaine (0.25%) can be mixed, but we do not recommend bupivacaine alone due to the longer onset of action and therefore the greater risk of pain during the procedure if started prior to onset of action.
- Some men are not appropriate candidates for prostate biopsy under local anesthesia and consideration of intravenous sedation in certain circumstances should be given:

- During a prostate biopsy patients should by assessed in real-time regarding their tolerance of the procedure. **If a patient is poorly tolerating the procedure, we recommend either re-administration of local anesthesia or aborting the procedure and scheduling the patient under intravenous sedation**

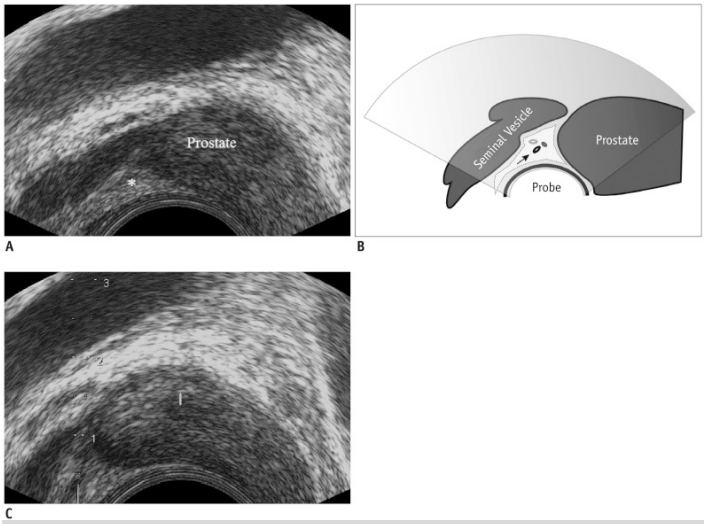

Figure 1

A. Ultrasound image in parasagittal plane showing triangular echogenic "Mount Everest sign" at site of neurovascular bundle (*). B. Schematic diagram demonstrating site of bi-basal injection in parasagittal plane (arrow). C. Parasagittal ultrasound image with biopsy trajectory guide-lines (dotted lines) to direct needle passage during bi-basal injections

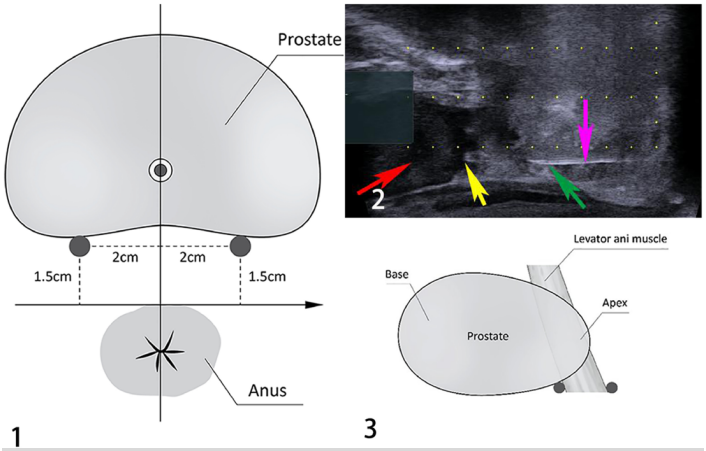

Figure 2

Approach to superficial perineal nerve block as described by Wang and colleagues.

How to block the BPN. (1) View of perineum in lithotomy position: the 2 black dots were the sites we punctured the anesthesia needle; (2) Sagittal transrectal ultrasound (TRUS) images: prostate (red arrow); prostate capsule where stop to inject lidocaine(yellow arrow); deep layer of superficial fascia where we start to inject lidocaine(green arrow); anesthesia needle(pink arrow); (3) Simplified diagram of sagittal transrectal ultrasound (TRUS) images of the plane of anesthesia needle insertion path: the 2 black dots were the sites we injected lidocaine. (Color version available online.)

2.1.3 Risks of Prostate Biopsy

- The **risks of prostate biopsy include vasovagal response (1%), hematuria (49%), hematospermia (36%), hematochezia (29%), UTI, anal pain, erectile dysfunction, and sepsis (transrectal 3%, transperineal <1%).**
- There is a 20-30% false negative rate of prostate biopsy. Men at risk for clinically meaningful prostate cancer should have close clinical follow-up.
- Prostate biopsy may also result in diagnosis of a clinically meaningless cancer (overdiagnosis) and prostate cancer treatments have additional risks (overtreatment).
- Prostate biopsy is associated with temporary erectile dysfunction. IIEF-5 scores declined by 4.6 points on average one month after prostate biopsy, but these effects were transient and not experienced by all men.[66]
- Current **AUA guidelines on antimicrobial prophylaxis guide the choice of antibiotic therapy with a recommended 24-hour dose of either a fluoroquinolone or 1st/2nd/3rd generation cephalosporin**.
  - Unfortunately, there is a **growing incidence of fluoroquinolone-resistance and extended beta-lactamase producing E. coli among men undergoing prostate biopsy**, with rate reported up to 50%.[42,43,44]
    - **Local antibiograms** can be useful in determining the appropriateness of antibiotic selection.
    - **Rectal swab culture** can also be employed to limit the risk of post-biopsy sepsis through the identification of fluoroquinolone resistant bacteria in the rectum.[67]
  - **Patients with artificial heart valves or joints may need additional prophylaxis.**

3. Prostate Cancer Risk Stratification

- PCa is a heterogeneous disease and treatment outcomes vary according to the aggressiveness of the cancer. The Gleason grade score, and grade groups can be used to define the tumor aggressiveness.[55]
  - **Gleason score is a summary grading system whereby 2 grades are reported, a primary grade (the most prevalent) and a secondary grade (highest grade), and then summed together.** In the current Gleason scoring system, the lowest grade reported is 3 and the highest is 5, resulting in a scale that goes from 6 to 10.
  - The **Gleason grade group system** is the currently recognized grading scale by the International Society of Urologic Pathologists (ISUP) and World Health Organization (WHO).[68] It is based on the Gleason score as follows:
    - Grade group 1: Gleason 3+3
    - Grade group 2: Gleason 3+4
    - Grade group 3: Gleason 4+3
    - Grade group 4: Gleason 8 (4+4, 3+5, or 5+3)
    - Grade group 5: Gleason 9-10 (4+5, 5+4, or 5+5)
  - The grade group system is easier for patients to understand and is clinically validated as a prognostic stratification system.[69]
- Once a diagnosis of PCa is made, **risk assessment** becomes paramount in guiding treatment decisions and for counseling patients accurately about expected oncologic and functional outcomes.[55]
  - Factors employed in risk stratification include:
    - **PSA at diagnosis**
    - **Clinical staging** based on rectal examination
    - **Gleason grade group**
  - Based on these risk factors patients can be categorized into risk groups.
- The **AUA utilizes a 3-tier risk stratification system** (**see table 4**) based on these risk factors. These risks groups can then be used to outline treatment options.[70]
- The **National Comprehensive Cancer Network (NCCN) utilizes a 6-tier system** based on the same risk factors (**see table 5**).[7] These risk factors are then used to recommend staging studies, genetic testing, and treatment options.
  - The NCCN and AUA guidelines provide comprehensive recommendations regarding the appropriate utilization of axial imaging, bone imaging, molecular imaging, germline genetic testing (germline), molecular testing of the tumor (somatic), and therapeutic guidance.
    - **Axial Imaging or Bone Scan** should be obtained for patients with high-risk prostate cancer. Axial Imaging can consist of abdominopelvic CT scan or MRI. **Molecular imaging (PET-CT)** can be considered for patients with high risk of metastatic disease.[71]
    - **Somatic testing**:
      - Men with >10-year life expectancy and localized low, favorable intermediate, unfavorable intermediate, and high-risk prostate cancer to inform the risk of adverse pathology (biopsy under-grading / under-staging) and prognosis.
      - Men with N1 and M1 disease for homologous recombination gene mutations, microsatellite instability, and mismatch repair deficiencies to guide treatment decision-making.

- **Germline testing**:
  - Men with very-high risk clinically localized, N1, or M1 disease (hormone-sensitive and castration-resistant) to identify potentially heritable genetic changes. This should be done in concert with a detailed family history and with trained genetic counselors (when available).
  - Men with a strong family history of prostate cancer or related cancers.[71]
- Additionally, there are numerous nomograms and other helpful tools for assessing risk and predicting PCa clinical outcomes.[72,73,74,75,76,77]
- Novel independent molecular/genetic risk prognostic tools are under development with the goal of advancing our risk prediction abilities.
- Additionally, risk calculators and nomograms are under development incorporating the data derived from prostate biopsy pathology obtained via MRI targeted biopsy sampling over the conventional systematic sampling schema from which most widely accepted and used nomograms have been created.[78,79,80,81,82]

Table 4: AUA Risk Stratification	
Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a
Intermediate Risk	PSA 10-<20 ng/ml OR Grade Group 2-3 OR clinical stage T2b-c • Favorable: Grade Group 1 (with PSA 10-<20) OR Grade Group 2 (with PSA<10) • Unfavorable: Grade Group 2 (with either PSA 10-<20 or clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)
High Risk	PSA >20 ng/ml OR Grade Group 4-5 OR clinical stage≥T3*
* Adapted from NCCN Guidelines Version 2.2019 (Mohler 2019)	

Table 5: NCCN Risk Stratification

Risk group	Clinical features
Very Low	T1c AND Grade Group 1 AND PSA <10 AND Fewer than 3 cores involved WITH ≤50% of core involvement AND PSA density <0.15
Low	T1-T2a AND Grade Group 1 AND PSA <10
Favorable Intermediate Risk	Grade Group 2 OR T2b-T2c (can be Grade Group 1) OR PSA 10-20 (can be Grade Group 1) AND <50% of total cores sampled positive
Unfavorable Intermediate Risk	Any combination of T2b-T2c, Grade Group 2, or PSA 10-20 OR Any Grade Group 3 or >50% of core positive
High Risk	T3a OR Grade group 4/5 OR PSA >20
Very High Risk	T3b-T4 OR Primary Gleason pattern 5 OR >4 cores Grade Group 4/5
* Adapted from NCCN Guidelines Version 2.2019 (Mohler 2019)	

4. Chemoprevention

Several large, randomized placebo-controlled trials have reported results of pharmacologic chemoprevention. Lifestyle modifications, including the use of vitamin supplements, have also been studied.

4.1 Clinical Trials

- **Prostate Cancer Prevention Trial (PCPT)**: designed to evaluate the effectiveness of finasteride in reducing the detection of PCa in men with low risk of disease (PSA<3 ng/ml).[83]
  - PCa was detected by biopsy (which included end-of study biopsies) in 24.4% of the study participants, and **finasteride decreased the overall relative risk of PCa by 25%**.
- **Reduction by Dutasteride of Prostate Cancer Events (REDUCE trial)** examined the effects of dutasteride in a higher risk cohor (PSA 2.5-10 ng/ml and negative prior biopsy), with a **similar relative risk reduction of 25% and an absolute reduction of 5.1%**[84]
- The **FDA Oncologic Drug Advisory Committee did not issue an indication for the prevention of PCa with either of these 5-alpha reductase inhibitors based on the PCPT and REDUCE results**. This decision was based largely on the premise that low-grade PCa poses little threat to health and should not be treated; therefore, preventing these cancers is of limited benefit. The Advisory Committee raised concerns that the risk of high-grade Gleason 8 to 10 cancers may be slightly increased in patients receiving these drugs.
- The **Selenium and Vitamin E Cancer Prevention Trial (SELECT)** randomized 35,533 men at low risk for PCa to regimens of either vitamin, or combinations of these agents.[85]
  - **No significant differences were found in rates of PCa across the intervention groups. Therefore, Selenium or Vitamin E is not recommended for the prevention of PCa.**
- The **Men's Eating and Living Study (CALBG 70807)** is a multi-centered phase III clinical trial that randomized patients to an intervention of increased vegetable consumption. Eligibility criteria included men on active surveillance for PSA < 10 ng/dl and Gleason 3+3 or Gleason 3+4 PCa. The primary outcome was clinical progression due to PSA elevation (> 10 ng/dl), PSA doubling time < 3 years, or > 25% of cores positive for PCa, >50% of any one core positive, and > Gleason 3+4 or more for men < 70 years old, or > Gleason 4+3 for men > 70 years old. The study recently completed enrollment of 478 patients.[86] In 2020, the MEALS study reported no significant reduction in prostate cancer progression amongst men randomized to the behavioral intervention to increase vegetable consumption compared to controls for the men managed by active surveillance.[87]

5. Life Expectancy

- **Prostate cancer is a disease of long duration with significant latency between the diagnosis and risk of PCa mortality. Given this latency, the competing risk of non-cancer death must be considered with evaluating a man at risk for PCa (screening) and those who are newly diagnosed.**
- Life expectancy estimates can help men make informed decisions about PCa screening and treatment. Most tools used to determine life expectancy typically do not factor in comorbidities, lifestyle factors, or family history which all influence longevity. Instead, they rely on population-wide estimates using age, gender, and sometimes race.[88,89] Recently, however, a calculator that incorporates comorbid conditions for estimating life expectancy to inform PCa screening and treatment decisions was developed. This tool reports **remaining life-years** rather than risk estimates.[90]

6. Abbreviations

1. AUA: American Urological Association
2. mpMRI: Multiparametric MRI
3. NCCN: National Compressive Cancer Network
4. PBx: Prostate Biopsy
5. PCa: Prostate Cancer
6. PSA: Prostate Specific Antigen
7. TRUS: Transrectal Ultrasound

7. Related AUA Learning

7.1 Podcasts:

1. **AUA2018 058IC - Management of Common Dilemmas in Prostate Cancer Diagnosis, Staging and Treatment**
2. **AUA2019 037IC Help Patients Decide On Prostate Cancer Screening And Treatment**

7.2 Update Series:

1. AUA Update Series 2017 (Volume 36), Lesson 26: “Prostate Cancer Screening: From Prostate Specific Antigen to Novel Detectior Strategies.”
2. AUA Update Series 2016 (Volume 35), Lesson 13: “The Emerging Role of Image Targeting in Contemporary Prostate Biopsy.”
3. AUA Update Series 2016 (Volume 35), Lesson 14: “Multiparametric Magnetic Resonance Imaging for Prostate Cancer.”
4. AUA Update Series 2019 (Volume 38), Lesson 14 : “Office Based Prostate Biopsy.”
5. AUA Update Series 2019 (Volume 38), Lesson 17: “Establishment of a Quality Assurance Framework for Introduction of Prostate Magnetic Resonance Imaging and Fusion Biopsy Programs.

Videos

Transperineal Prostate Biopsy Demonstration

MRI-TRUS Fusion Prostate Biopsy

MRIUS Fusion Guided Prostate Biopsy Step-by-Step

Office-Based Transperineal Prostate Biopsy

MRI Fusion Transperineal Prostate Biopsy

LATP using the Precision Point™ Access System: a step-by-step video

V8-02: FREE HAND TRANSPERINEAL ULTRASOUND GUIDED PROSTATE BIOPSY

V3-02: Freehand Transperineal Prostate Biopsy Under Local Anesthesia

V6-11: Magnetic Resonance Imaging/Transrectal Ultrasound (MRI/TRUS) Fusion Guided Biopsy of the Prostate to Detect High Grade Cancer

V6-06: Use of MRI/US fusion for targeted prostate biopsy in Active Surveillance

Presentations

Prostate Cancer Presentation 1

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