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EARLY DETECTION OF PROSTATE CANCER: AUA/SUO GUIDELINE (2023)

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SUMMARY

Purpose

The recommendations discussed on the early detection of prostate cancer provide a framework to facilitate clinical decision-making in the implementation of prostate cancer screening and follow-up.

Methodology

The systematic review of this guideline was based on searches in Ovid MEDLINE and Embase and Cochrane Database of Systematic Reviews (January 1, 2000 – November 21, 2022). Searches were supplemented by reviewing reference lists of relevant articles. Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. The target population was persons without a diagnosis of prostate cancer undergoing prostate-specific antigen (PSA) screening, or patients without prostate cancer who have a suspicious finding indicating possible clinically significant prostate cancer and are undergoing or considering an initial or repeat biopsy.

GUIDELINE STATEMENTS

PSA SCREENING

1. Clinicians should engage in shared decision-making (SDM) with people for whom prostate cancer screening would be appropriate and proceed based on a person's values and preferences. (*Clinical Principle*)
2. When screening for prostate cancer, clinicians should use PSA as the first screening test. (*Strong Recommendation; Evidence Level: Grade A*)
3. For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (*Expert Opinion*)
4. Clinicians may begin prostate cancer screening and offer a baseline PSA test to people between ages 45 to 50 years. (*Conditional Recommendation; Evidence Level: Grade B*)

5. Clinicians should offer prostate cancer screening beginning at age 40 to 45 years for people at increased risk of developing prostate cancer based on the following factors: Black ancestry, germline mutations, strong family history of prostate cancer. (*Strong Recommendation; Evidence Level: Grade B*)
6. Clinicians should offer regular prostate cancer screening every 2 to 4 years to people aged 50 to 69 years. (*Strong Recommendation; Evidence Level: Grade A*)
7. Clinicians may personalize the re-screening interval, or decide to discontinue screening, based on patient preference, age, PSA, prostate cancer risk, life expectancy, and general health following SDM. (*Conditional Recommendation; Evidence Level: Grade B*)
8. Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer. (*Conditional Recommendation; Evidence Level: Grade C*)
9. For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy. (*Strong Recommendation; Evidence Level: Grade B*)
10. Clinicians and patients may use validated risk calculators to inform the SDM process regarding prostate biopsy. (*Conditional Recommendation; Evidence Level: Grade B*)
11. When the risk of clinically significant prostate cancer is sufficiently low based on available clinical, laboratory, and imaging data, clinicians and patients may forgo near-term prostate biopsy. (*Clinical Principle*)

INITIAL BIOPSY

12. Clinicians should inform patients undergoing a prostate biopsy that there is a risk of identifying a cancer with a sufficiently low risk of mortality that could safely be monitored with active surveillance (AS) rather than treated. (*Clinical Principle*)
13. Clinicians may use magnetic resonance imaging (MRI) prior to initial biopsy to increase the detection of Grade Group (GG) 2+ prostate cancer. (*Conditional Recommendation*; *Evidence Level: Grade B*)
14. Radiologists should utilize PI-RADS in the reporting of multi-parametric MRI (mpMRI) imaging. (*Moderate Recommendation; Evidence Level: Grade C*)
15. For biopsy-naïve patients who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy. (*Moderate Recommendation [targeted biopsies]/Conditional Recommendation [systematic template biopsy]; Evidence Level: Grade C*)
16. For patients with both an absence of suspicious findings on MRI and an elevated risk for GG2+ prostate cancer, clinicians should proceed with a systematic biopsy. (*Moderate Recommendation; Evidence Level: Grade C*)
17. Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (*Conditional Recommendation*; *Evidence Level: Grade C*)
18. For patients with a PSA > 50 ng/mL and no clinical concerns for infection or other cause for increased PSA (e.g., recent prostate instrumentation), clinicians may omit a prostate biopsy in cases where biopsy poses significant risk or where the need for prostate cancer treatment is urgent (e.g., impending spinal cord compression). (*Expert Opinion*)

REPEAT BIOPSY

19. Clinicians should communicate with patients following biopsy to review biopsy results, reassess risk of undetected or future development of GG2+ disease, and mutually decide whether to discontinue screening, continue screening, or perform adjunctive testing for early reassessment of risk. (*Clinical Principle*)

20. Clinicians should not discontinue prostate cancer screening based solely on a negative prostate biopsy. (*Strong Recommendation; Evidence Level: Grade C*)

21. After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy. (*Strong Recommendation; Evidence Level: Grade B*)

22. If the clinician and patient decide to continue screening after a negative biopsy, clinicians should re-evaluate the patient within the normal screening interval (two to four years) or sooner, depending on risk of clinically significant prostate cancer and life expectancy. (*Clinical Principle*)

23. At the time of re-evaluation after negative biopsy, clinicians should use a risk assessment tool that incorporates the protective effect of prior negative biopsy. (*Strong Recommendation; Evidence Level: Grade B*)

24. After a negative initial biopsy in patients with low probability for harboring GG2+ prostate cancer, clinicians should not reflexively perform biomarker testing. (*Clinical Principle*)

25. After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. (*Conditional Recommendation; Evidence Level: Grade C*)

26. In patients with focal (one core) high-grade prostatic intraepithelial neoplasia (HGPIN) on biopsy, clinicians should not perform immediate repeat biopsy. (*Moderate Recommendation; Evidence Level: Grade C*)

27. In patients with multifocal HGPIN, clinicians may proceed with additional risk evaluation, guided by PSA/DRE and mpMRI findings. (*Expert Opinion*)

28. In patients with atypical small acinar proliferation (ASAP), clinicians should perform additional testing. (*Expert Opinion*)

29. In patients with atypical intraductal proliferation (AIP), clinicians should perform additional testing. (*Expert Opinion*)

30. In patients undergoing repeat biopsy with no prior prostate MRI, clinicians should obtain a prostate MRI prior to biopsy. (*Strong Recommendation; Evidence Level: Grade C*)

31. In patients with indications for a repeat biopsy who do not have a suspicious lesion on MRI, clinicians may proceed with a systematic biopsy. (*Conditional Recommendation; Evidence Level: Grade B*)

32. In patients undergoing repeat biopsy and who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy. (*Moderate Recommendation [targeted biopsies]/Conditional Recommendation [systematic template biopsy]; Evidence Level: Grade C)*

BIOPSY TECHNIQUE

33. Clinicians may use software registration of MRI and ultrasound images during fusion biopsy, when available. (*Expert Opinion*)
34. Clinicians should obtain at least two needle biopsy cores per target in patients with suspicious prostate lesion(s) on MRI. (*Moderate Recommendation; Evidence Level: Grade C*)
35. Clinicians may use either a transrectal or transperineal biopsy route when performing a biopsy. (*Conditional Recommendation; Evidence Level: Grade C*)

INTRODUCTION

PURPOSE

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in American men. It is estimated that 288,300 patients will be diagnosed with prostate cancer and 34,700 deaths from prostate cancer in the United States (U.S.) in 2023, and an estimated 1,276,106 new cases and 358,989 deaths worldwide reported in 2018.[1, 2] Significant advances have been made in early detection, especially with the increasing availability and usage of biomarkers as well as mpMRI. This guideline addresses early detection with an emphasis on PSA-based screening, considerations for initial and repeat biopsy, and biopsy technique based on a systematic review of the recently published literature, with the goal of identifying clinically significant prostate cancer.

Terminology and Definitions

This guideline provides recommendations for prostate cancer screening in different groups based on their age range and risk criteria, with an emphasis on SDM. SDM is particularly necessary as there is no universally accepted standard definition of low versus elevated risk for prostate cancer detection. In practice, clinicians often resort to an elevated PSA level based on laboratory, prostate size, or age-based "norms" as a surrogate for an elevated prostate cancer risk, but such definitions, while easy to apply, do not suffice for all people and circumstances. Thus, clinicians may tailor the definitions of elevated risk and elevated PSA to the clinical situation at hand. Some examples that may elevate risk of clinically significant prostate cancer are Black ancestry, germline mutations, strong family history of prostate cancer, and other factors that may be indicated by risk calculators (e.g., total PSA, PSA density, percent free PSA, age). More importantly, this guideline emphasizes potential benefit in using validated risk calculators and provides recommendations for the timing and methodology for screening.

This guideline underscores the goal of detecting "clinically significant" cancer for initial and repeat biopsy. The risk of mortality in patients with GG1 prostate cancer is extremely low.[3, 4] Thus, this guideline defines clinically significant prostate cancer as GG2 or higher (GG2+) prostate cancer and will use "clinically significant prostate cancer" and "GG2+" interchangeably throughout. However, the Panel acknowledges there are various definitions of "clinically significant" as not all "clinically significant" cancers are destined to impact quality or quantity of life, and it is patient-specific. The guideline recommends utilizing validated risk calculators, particularly calculators that incorporate previous negative biopsy and mpMRI use in the repeat biopsy setting. It also addresses the significance of non-cancerous, yet potentially significant, pathologic findings identified from the biopsy. With the emergence of mpMRI and novel biomarkers, the Panel evaluated the current evidence to develop recommendations on how best to incorporate these into clinical practice. In certain clinical scenarios, additional data are needed to make definitive recommendations for the optimal biopsy approach. An abnormal MRI, for the purpose of this guideline, is defined as PI-RADS 3 to 5 as supported by much of the literature. However, given the local variation and expertise in reading MRIs, some clinicians may opt to limit an abnormal MRI to PI-RADS 4 to 5.

This guideline is intended for all patient populations with a prostate gland. For consistency purposes, this guideline refers to these individuals as "people" or "patients" throughout this document.

METHODOLOGY

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the Early Detection of Prostate Cancer Panel.

Panel Formation

The Panel was created in 2021 by the American Urological Association Education and Research, Inc. (AUAER). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members with specific expertise in this area. The multidisciplinary panel includes representation from urology/urologic oncology, epidemiology, biostatistics, primary care, pathology, and radiology. The Panel additionally included patient representation. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

Searches and Article Selection

A search was conducted for existing systematic reviews on October 11, 2021 and updated on November 21, 2022. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. An electronic search employing Ovid was used to systematically search the MEDLINE and Embase databases, as well as the Cochrane Library, for systematic reviews evaluating detection of prostate cancer.

When systematic reviews were not identified, or when identified reviews were incomplete, Ovid was used to systematically search MEDLINE and Embase databases for articles evaluating detection of prostate cancer utilizing the PICO elements. During PICO development, panel members submitted landmark studies addressing the Key Questions to the methodologist. These studies were defined as control articles and were compared with the literature search strategy output; the strategy was subsequently updated as necessary to capture all control articles. Databases were originally searched for studies published from January 1, 2000 through October 11, 2021 and subsequently updated to November 21, 2022. In addition to the MEDLINE and Embase database searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

All hits from the Ovid literature search were input into reference management software (EndNote X7), where duplicate citations were removed. Abstracts were reviewed by the methodologist to determine if each study addressed the Key Questions and met study design inclusion criteria. For all research questions, randomized controlled trials (RCTs), observational studies, modelling studies with theoretical cohorts, and case-control studies were considered for inclusion in the evidence base. For all Key Questions, studies had to enroll at least 30 patients per study arm. Case series, letters, editorials, *in vitro* studies, studies conducted in animal models, and studies not published in English were excluded from the evidence base *a priori*.

Full-text review was conducted on studies that passed the abstract screening phase. Studies were compared to the PICO criteria as outlined below. Ten panel members were paired with the methodologist and completed duplicate full-text study selection of 10% of studies undergoing full-text review. The dual-review trained the methodologist, who then completed full-time review of the remaining studies.

Data Abstraction

Data were extracted from all studies that passed full-text review by the methodologist.

Risk of Bias Assessment

Quality assessment for all retained studies was conducted. Using this method, studies deemed to be of low quality would not be excluded from the systematic review, but would be retained, and their methodological strengths and weaknesses were discussed where relevant. To evaluate the risk of bias within the identified studies, the Assessment of Multiple Systematic Reviews (AMSTAR),[5] tool was used for systematic reviews, the Cochrane Risk of Bias Tool[6] was used for randomized studies, a Risk of Bias in Non-Randomized Studies of Intervention (ROBINS-I)[7] was used for observational studies and modeling studies with theoretical cohorts, and Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[8] was used for diagnostic accuracy studies.

Additional important quality features, such as comparison type, power of statistical analysis, and sources of funding were extracted for each study.

Data Synthesis

Meta-analysis was appropriate for studies informing four Key Questions and six outcomes using RevMan.[9] For all meta-analyses there was substantial heterogeneity in both the patient populations and the methodologies employed within the studies, making random-effects methods the most appropriate. Odds ratios for detection of clinically significant prostate cancer using MRI-targeted biopsy alone and fusion biopsy plus systematic biopsy were calculated based on raw data reported in studies and pooled using an inverse-variance method. For calculation of the number of avoided biopsies and missed clinically significant prostate cancer using various biomarkers in both biopsy naïve and repeat biopsy populations, prevalence and standard errors were extracted or calculated from reported raw data in studies and pooled using an inverse variance method. Finally, prevalence and standard errors for clinically significant prostate cancer detection using a PI-RADS score of 1 to 2, 3, 4, and 5 were calculated from raw data reported in studies and pooled using an inverse-variance method.[9] Due to the paucity of data using only PI-RADS version 2.1, pooled studies used version 1.0 through version 2.1.

Determination of Evidence Strength

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[10] system was used to determine the aggregate evidence quality for each outcome, or group of related outcomes, informing Key Questions. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence, is correct. Evidence is categorized as high, moderate, low, and very low, and assessment is based on the aggregate risk of bias for the evidence base, plus limitations introduced as a consequence of inconsistency, indirectness, imprecision, and publication bias across the studies.[11] Additionally, certainty of evidence can be downgraded if confounding across the studies has resulted in the potential for the evidence base to overestimate the effect. Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding would suggest either spurious effects or would reduce the demonstrated effect.

The AUA employs a 3-tiered strength of evidence system to underpin evidence-based guideline statements. **Table 1** summarizes the GRADE categories, definitions, and how these categories translate to the AUA strength of evidence categories. In short, high certainty by GRADE translates to AUA A-category strength of evidence, moderate to B, and both low and very low to C.

Table 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

The AUA categorizes body of evidence strength as Grade A (e.g., well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (e.g., RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (e.g., RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[12]

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (**Table 2**). Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Moderate Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. Conditional Recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences in opinion emerged.[13] A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a comprehensive peer review process to ensure that the document was reviewed by experts who were knowledgeable in the area of early detection of prostate cancer. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by external content experts. Additionally, a call for reviewers was placed on the AUA website from October 10 to 24 of 2022 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and members of the AUA Patient Advocacy network to open the document further to the patient perspective. The draft guideline document was distributed to 174 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 84 reviewers provided comments, including 69 external reviewers. At the end of the peer review process,

a total of 770 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted to the AUA PGC, SQC, and BOD for final approval as well as SUO.

Table 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Guideline Statements

PSA SCREENING

1. **Clinicians should engage in SDM with people for whom prostate cancer screening would be appropriate and proceed based on a person's values and preferences. (*Clinical Principle*)**

Prostate cancer screening is a preference-sensitive decision. For this reason, the Panel recommends clinicians engage in SDM with people considering prostate cancer screening so they can make an informed choice. The Panel discourages the practice of ordering a PSA test without informing the patient upfront, and likewise discourages the practice of failing to inform the patient of the availability of PSA screening, as appropriate.

SDM is considered state-of-the art in patient counseling for preference-sensitive decisions.[14] This practice can be facilitated using a decision aid. A 2017 Cochrane systematic review and meta-analysis of 105 studies showed that people who view decision aids feel more knowledgeable, better informed, and clearer about their values.[15] A 2019 systematic review and meta-analysis of 19 RCTs evaluating decision aids specifically designed for the prostate cancer screening decision versus conventional care showed a small decrease in decisional conflict (moderate-quality evidence) and a small increase in knowledge (low-quality evidence). However, there was no association between clinician and patient discussion on prostate cancer screening or discussion on the type of screening to obtain.[16]

While SDM is strongly encouraged, the Panel acknowledges that downstream risks of screening of potential side-effects from curative treatment of screen-detected tumors are lower today with increased utilization of AS for low-risk disease. This is currently a practice endorsed by the AUA as a strong recommendation for patients with low-risk localized prostate cancer.[17]

A 2016 AUA White paper[14] recommends SDM which include four key elements:

1. Involvement of both the clinician and the patient in the decision-making process.
2. Sharing information by both the clinician and the patient.
3. Building consensus through the expression of preferences by both clinician and patient.
4. Agreement by both the clinician and patient on the decision to implement.

2. **When screening for prostate cancer, clinicians should use PSA as the first screening test. (*Strong Recommendation; Evidence Level: Grade A*)**

The PSA blood test remains the first-line screening test of choice based on randomized trials of PSA-based screening showing reductions in metastasis and prostate cancer death.[18, 19] At the time of this evidence review, very limited evidence has emerged regarding other candidates for first-line biomarkers or imaging.

Stockholm-3 (STHLM-3) has been evaluated as a first-line screening test for predicting the risk of GG2+ prostate cancers. The STHLM-3 test is a multiplex test combining clinical variables (age, first-degree family history of prostate cancer, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free to total PSA, hK2, MIC-1, and MSMB), and a polygenic risk score (PRS). The STHLM-3 test has a higher predictive accuracy compared to PSA alone (area under the curve [AUC] 0.74 versus 0.56) and reduced unnecessary biopsies by 32%.[20] Using the STHLM-3 test and performing targeted plus systematic biopsies only in patients with MRI-suspicious lesions decreased overdetection and maintained the number of high-grade cancers found, as compared to systematic biopsy alone, in a screening-by-invitation trial.[21, 22] While this novel test appears promising, further validation in diverse populations to confirm these findings will be necessary to move forward into practice.

PRSs that are based on single nucleotide polymorphisms (SNPs) are genetic tests used to predict a person's risk of developing prostate cancer. Various combinations of SNPs have been aggregated to produce several commercially available options. There is little evidence to mandate which SNP panel or PRS to use and where to threshold risk to create strata with different screening intensities. The endpoint of the studies on PRS has mainly focused on any detection of prostate cancer, not clinically significant prostate cancer. At the time of this evidence review, no PRS tool has been shown to

discriminate between aggressive and indolent prostate cancer risk.[23] Calculating a PRS based on genotypes of 66 known prostate cancer loci for 4,967 patients in the Finnish European Randomized Study of Screening for Prostate Cancer (ERSPC), the rate of overdiagnosis (e.g., detection of GG1) of screen-detected cancers was 42%, with 58% of these found in the lower PRS risk group and 37% in those with higher PRS risk.[24] Adding SNPs to STHLM-3 added only 1% to the AUC (from 0.75 to 0.76) for GG2+ (Gleason Score ≥ 7) after the clinical information and protein biomarkers.[25] The BARCODE-1 pilot trial invited patients to prostate cancer screening using a PRS score but had a low participation rate (26% of 1,436 patients invited).[26] This large-scale trial is ongoing.

3. For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (*Expert Opinion*)

In people with a newly elevated PSA, it will return to a normal level in 25% to 40% upon retesting.[27] Among 1,686 biopsied patients in the STHLM-3 study with a PSA of 3 to 10 ng/mL, and 2 PSA tests 8 weeks apart, 283 (17%) subsequently had a PSA < 3 ng/mL. Given the clear evidence that PSA tests may normalize, it would be prudent to confirm a newly elevated PSA test before proceeding with further work up.[28]

The Panel also strongly supports the Choosing Wisely AUA initiative (https://www.choosingwisely.org/clinician-lists/american-urological-association-treating-elevated-psa-with-antibiotics/) that empiric antibiotics should not be utilized to treat an elevated PSA in an asymptomatic person.[29, 30] Neither DRE nor bicycle riding appreciably alters the PSA,[31, 32] and most controlled studies evaluating ejaculation suggest it either does not significantly impact or modestly increases (~10%) PSA.[33] The half-life of PSA is 2 to 3 days. A repeat PSA in a few months is recommended, though it can be shortened or lengthened depending on other clinical factors. Clinicians should also recognize that urinary tract infections and instrumentation (e.g., recent bladder catheterization, prostate biopsy or cystoscopy, urinary retention) cause transient increases in PSA. PSA elevations in these settings should be repeated after appropriate time periods to allow for PSA to reach baseline level.

The definition of an elevated PSA has changed over time. The commonly cited threshold of 4 ng/mL is based on very early studies that identify the highest levels typically observed among patients thought to be free of prostate cancer. Another cited threshold of 3 ng/mL is taken from the ERSPC trial of prostate cancer screening that showed a significant reduction in prostate cancer deaths among patients who entered the trial between ages 55 to 69 years and were referred to biopsy based on that threshold. The knowledge that PSA generally increases with age in people without prostate cancer has led to the consensus that the threshold above which a PSA level should be considered elevated should increase with age, and that the original threshold of 4 ng/mL is too high for people in their 40s and 50s and too low for people in their 70s and 80s who have a high risk of overdiagnosis. Most studies identifying age-varying thresholds specify threshold values of 2.5 ng/mL for people in their 40s, 3.5 ng/mL for people in their 50s, 4.5 ng/mL for people in their 60s, and 6.5 ng/mL for people in their 70s.[34-36]

4. Clinicians may begin prostate cancer screening and offer a baseline PSA test to people between ages 45 to 50 years. (*Conditional Recommendation; Evidence Level: Grade B*)

For people at average risk of developing prostate cancer, there is no randomized evidence showing a benefit to initiation of routine screening for prostate cancer before 45 years of age. The randomized trials that demonstrate a benefit for prostate cancer screening (Goteborg-1[37] and ERSPC[18]) began at ages 50 and 55 years, respectively.

The earlier initiation of screening is supported by observational studies that have demonstrated a prognostic value of obtaining a baseline PSA in early midlife.[38, 39] A review of eight PSA studies in younger people have shown baseline PSA measurements were robust predictors of aggressive prostate cancer, metastasis, and disease-specific mortality many years later. Baseline PSA was a stronger predictor of prostate cancer risk than race and family history of prostate cancer. Median PSA levels ranged from ~0.4 to 0.7 ng/mL in patients in their 40s and from ~0.7 to 1 ng/mL in patients in their 50s.[38]

The prevalence of prostate cancer is low among patients aged 40 to 45 years. The modeling studies comparing various start ages have shown that lowering the screening start age to 40 to 45 years instead of 50 to 55 years slightly increased the probability of lives saved, but substantially increased the number of PSA tests.[34]

In the Malmö Preventive Project, the risk of prostate cancer metastases by 15 years' follow-up was low (0.6%) for patients with PSA in the highest percentile (≥ 1.3 ng/mL) at 40 years of age. For patients aged 45 to 49 years with PSA below the median (0.68 ng/mL), the risk of prostate cancer metastasis within 25 years was 0.85%. Patients with PSA in the highest decile (≥ 1.6 ng/mL) at ages 45 to 49 years contributed to nearly half of prostate cancer deaths over the next 25 to 30 years.[39]

A randomized trial of risk-adapted screening for prostate cancer comparing patients starting at age 45 versus 50 years (the PROBASE trial) is currently ongoing, with 23,301 patients having participated in screening in the first round of the trial.[40] The participation rate was low (20%), and 35% with indication for biopsy refused to undergo the procedure. The prevalence of screen-detected prostate cancer in 45-year-old patients was very low (0.2%), and only 4 patients were diagnosed with aggressive prostate cancer GG3 or higher. Thus, the use of SDM is highly recommended given the uncertainty involved.

5. **Clinicians should offer prostate cancer screening beginning at age 40 to 45 years for people at increased risk of developing prostate cancer based on the following factors: Black ancestry, germline mutations, strong family history of prostate cancer. (*Strong Recommendation; Evidence Level: Grade B*)**

If a person has risk factors associated with an increased risk of developing prostate cancer (including Black ancestry, germline mutations, strong family history of prostate cancer), in particular if they have an increased risk of metastatic disease, an earlier age to begin screening may be appropriate in addition to a shorter re-screening interval.[41]

Black individuals have a disproportionate cancer burden and a two-fold higher risk of death from prostate cancer compared to White individuals.[42] A study using three models discovered that patients who self-identify as Black appear to have earlier age of onset and increased risk of metastases before clinical diagnosis.[43] This study found the risk of a Black patient developing fatal prostate cancer, if not diagnosed, reached the same level as that of the general population three to nine years earlier, informing the proposal that Black patients initiate screening approximately five to ten years prior to the recommendation for average-risk individuals.[43] This increased risk may be addressed by screening Black patients more frequently (e.g., annually), but the risk of overdiagnosis among older Black patients is considerably higher than the average-risk population, making SDM and personalized screening particularly important.

Empirical studies have shown patients with germline *BRCA1* and *BRCA2* variants have increased risks of both disease onset and progression.[44] The IMPACT study revealed a high positive predictive value (PPV) of PSA screening (with biopsy referral threshold 3 ng/mL) in these patients and a high frequency of clinically significant cancers,[45] particularly among *BRCA2* carriers.[46] The IMPACT study showed a stronger relationship (eight-fold increased risk) between *BRCA2* carriers and aggressive cancer for whom systematic PSA screening is indicated, while further study is needed to determine the role of screening among *BRCA1* mutation carriers.[46] Similarly, mutations in *ATM, MLH1, MSH2, MSH6, PMS2, HOXB13, NBS1,* and *CHEK2* need further study. In the IMPACT study, after one screening round, carriers of pathogenic variants in mismatch-repair genes *MSH2* and *MSH6* had a higher risk of prostate cancer compared with age-matched non-carrier controls, potentially supporting screening of these patients.[44] These patients may benefit from both earlier initiation of PSA screening and shorter intervals between screenings.

Although there is no standard definition of strong family history, several guidelines and consensus statements propose common criteria that include: 1) people with one brother or father or two or more male relatives with one of the following: a) diagnosed with prostate cancer at age < 60 years; b) any of whom died of prostate cancer; c) any of whom had metastatic prostate cancer. 2) family history of other cancers with two or more cancers in hereditary breast and ovarian cancer syndrome or Lynch syndrome spectrum.[47, 48]

Studies have consistently found elevated risk of prostate cancer in patients with a family history of prostate cancer[49-52] and also in patients with a family history of prostate and breast cancer.[53, 54] In some studies, the observed increase in risk may be partly due to detection bias associated with greater compliance to screening and biopsy[50] among patients with a known family history. Some studies have differentiated low- and high-risk prostate cancers associated with family history[51, 52] and

have suggested focusing on the association between family history and high-risk cancer as more relevant for making screening recommendations. Patients with a strong family history (e.g., two or more first-degree relatives have a four-fold relative risk compared to those without a family history[49]) should ideally be genotyped to ascertain whether this is associated with a pathogenic variant (e.g., *BRCA1/2*, Lynch Syndrome, *ATM*, *CHEK2*) or one or more of a growing set of identified germline DNA damage-repair mutations found in patients with metastatic prostate cancer diagnoses.[55] In the absence of this information, patients with a strong family history may be screened earlier and/or more frequently, similar to those with detected germline pathogenic variants. Again, SDM is highly recommended given the uncertainty involved in the PSA screening setting.

6. **Clinicians should offer regular prostate cancer screening every 2 to 4 years to people aged 50 to 69 years. (*Strong Recommendation; Evidence Level: Grade A*)**

Two RCTs, ERSPC[18] and the Goteborg population-based prostate cancer screening trial (Goteborg-1),[37] provide evidence that regular PSA screening every 2 to 4 years in patients aged 50 to 69 years reduces the risk of metastatic prostate cancer and prostate cancer mortality at 16 to 22 years, compared to no or opportunistic screening. The Goteborg-1 trial was designed separately from ERSPC with a separate power calculation and included patients 50 to 64.[56] Patients aged 55 to 69 years were later included in ERSPC.

The number needed to be screened (NNS, the inverse of the absolute risk reduction in prostate cancer mortality) and number needed to be diagnosed (NND, additional cases diagnosed) to prevent one death from prostate cancer depends on the screening protocol (including screening ages) and follow-up time **(Table 3)**.

Table 3: Number Needed to Screen (NNS) and Additional Number Needed to Diagnose (NND) to Prevent One Death from Prostate Cancer by Study

Study	Screen Ages	Follow up time	Protocol	NNS	NND
ERSPC[18]	55-69	16 years	2-4 years Bx PSA > 3 ng/mL	570	18
ERSPC (2009)[57]	50-74	9 years	2-4 years Bx PSA > 3 ng/mL	1,410	48
Goteborg-1[37]	50-64	22 years	2 years Bx PSA 2.5-3 + ng/mL	221	9
ERSPC modeling study[58]	55-69	Lifetime horizon	Annual Bx PSA 3 + ng/mL 4 years	98 129	5 5
U.S. modeling study[34]	50-69	Lifetime horizon	2 years Bx PSA 4 + ng/mL Bx PSA 2.5 + ng/mL	 243 204	 3 4
(Abbreviations: Bx, biopsy; PSA, prostate-specific antigen)					

A study comparing patients 60 years of age who have been screened every 2 years in the Goteborg-1 trial, compared to unscreened patients 60 years of age in the Malmö Preventive Project, showed that continuing to screen patients with PSA ≥ 2 ng/mL at 60 years of age had a favorable net-benefit in terms of reducing risk of prostate cancer metastasis and mortality at 15 years. At 15 years, the NNS to prevent 1 death from prostate cancer was 23 and NND was 6.[59]

The U.S. Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial was unable to demonstrate a statistically significant difference in prostate cancer mortality at 17 years of follow-up between patients randomized to screening versus usual care.[60] However, the control group had a high degree of PSA testing (contamination) with more than 80% of patients receiving at least 1 PSA test during the trial.[61] In later years, patients in the control groups of ERSPC and Goteborg-1 have also been exposed to PSA testing. In PLCO, the cut-off for biopsy was higher than in ERSPC (4 versus 3 ng/mL), the proportion of patients with elevated PSAs that were biopsied was lower (34% versus over 90%) and screening stopped after 6 years. Taking differences in implementation into account, a modeling study aiming to reconcile PLCO and ERSPC showed PSA screening versus no screening can reduce prostate cancer mortality by approximately 30% at 11 to 13 years.[62]

A modeling study primarily based on ERSPC compared the benefits and harms of annual PSA screening of patients aged 55 to 69 years. Over a life-time horizon with a PSA threshold of 3 ng/mL, screening would lead to 9 fewer deaths from prostate cancer for every 1,000 screened. The NNS to prevent 1 death from prostate cancer over a lifetime horizon was 98, and the NND was 5. Overall, screening was offset by a 23% reduction in quality-adjusted life years from life years gained, mainly owing to long-term side-effects from treatment.[58] A U.S. model produced similarly low NND[34] in evaluation of screening between ages 50 and 69 years using a PSA threshold of 4 ng/mL, which had been standard practice in the U.S. Again, SDM is highly recommended given the uncertainty involved in the PSA screening setting.

7. **Clinicians may personalize the re-screening interval, or decide to discontinue screening, based on patient preference, age, PSA, prostate cancer risk, life expectancy, and general health following SDM. (*Conditional Recommendation; Evidence Level: Grade B*)**

The randomized trials (PLCO, Goteborg-1, ERSPC) screened patients aged 50 to 69 years every 1 to 4 years and demonstrated a reduction in prostate cancer mortality. However, increasing evidence from additional analyses of the randomized trials, observational studies, and modeling studies show the balance between benefits (reduction in metastatic prostate cancer and prostate cancer mortality) and harms (anxiety, false positives, overdiagnosis, side-effects from prostate biopsy) of screening can be modulated through personalized risk-stratified screening approaches.[34, 39, 59, 63-68]

Risk-stratified re-screening intervals and biopsy thresholds may be tailored for select patients

The re-screening interval can be 1 to 4 years for patients with PSA levels of 1 to 3 ng/mL between the ages of 45 to 70 years, while the re-screening interval can be prolonged for patients aged 45 to 70 years with a PSA < 1 ng/mL or those with a PSA below the age-specific median.[58, 63, 69] Studies have shown that patients in the age range of 40 to 59 years with a PSA below the age-specific median, without a strong family history of prostate cancer, and no known pathogenic germline mutation, have a very low risk of metastatic cancer or long-term prostate cancer mortality. In a case-control study conducted in Sweden (Malmö Preventive Project cohort),[39] among patients aged 40 to 55 years, the 15-year risk of metastasis for patients with PSA below the median at ages 45 to 49 years was 0.09%, and below the median at ages 51 to 55 years was 0.23%. In a U.S. case-control study (Physicians' Health Study cohort)[67] among patients 40 to 59 years of age, 82%, 71%, and 86% of lethal cases occurred in patients with PSA above the median at ages 40 to 49 years (median PSA 0.68 ng/mL), 50 to 54 years (median PSA 0.88 ng/mL), and 55 to 59 years (median PSA 0.96 ng/mL), respectively. Both studies suggest risk-stratified screening based on midlife PSA and should be considered in patients aged 45 to 59 years. However, they do not explicitly evaluate potential harm-benefit implications of any specific strategies. There were 2 models[70] used to examine the impact of

lengthening the interval between PSA tests to 8 years from a baseline interval of 2 years for patients with a PSA < 1.0 ng/mL at 45 years of age. Compared with biennial screening from ages 45 to 69 years, this risk-stratified approach led to half the number of tests while preserving more than 95% of the lives saved.

Comparing 35 different screening strategies, a modeling study showed that PSA screening strategies using higher thresholds for biopsy referral for older patients, and screening patients with low PSA levels less frequently reduced the harms of screening (false positives, overdiagnoses) while saving the majority of lives with standard intervals (e.g., annual or biennial screening).[34]

Patients with low PSA

Amongst patients 60 years of age with a PSA < 1 ng/mL (age-specific median), the 25-year risk of metastases or death from prostate cancer in a largely *unscreened* population (Malmö Preventive Project) is extremely low (0.5% and 0.2%, respectively).[64] These empiric findings are supported by modeling data that suggest a higher likelihood of death from prostate cancer if screening were discontinued in these patients (5% to 13.1% fewer lives saved compared with continuing screening to 69 years of age);[70] therefore, it is reasonable to significantly lengthen the re-screening interval or discontinue screening based on SDM provided there are no other risk factors, such as strong family history of prostate cancer.[59, 64, 70]

In comparison of regularly screened patients in the Goteborg-1 trial versus unscreened people 60 years of age in the Malmö Preventive Project with PSA < 2 ng/mL, continued screening every 2 years for 15 years found an increase in prostate cancer incidence (7.7%) without a decrease in prostate cancer mortality.[59] For patients with PSA ≥ 2 ng/mL, the reduction in cancer mortality for screened patients was large with 23 patients being screened (NNS) and 6 diagnosed (NND) to prevent 1 prostate cancer death at 15 years.[59]

Older patients

The decision to screen patients should be an SDM conversation predicated upon a person's prior PSA levels and general health, and a flexible age to discontinue screening may be based on individualized decision-making to balance detection of aggressive cancers and overdiagnosis. This is particularly important in people between the ages of 70 to 80 years where there is a higher risk of competing mortality.[71, 72] Clinicians may discontinue or substantially lengthen the re-screening interval for patients 75 years of age or older if PSA is < 3 ng/mL. In the Baltimore Longitudinal Study of Aging, patients 75 years or older with a PSA < 3 ng/mL were unlikely to be diagnosed with aggressive prostate cancer, and no patients between the ages of 75 to 80 years with a PSA < 3 ng/mL died of prostate cancer during their remaining lifetime.[73]

A modeling study[74] found that discontinuing screening at ages 66 and 72 years for patients with severe and moderate comorbidity, respectively, resulted in similar harms and benefits compared to screening people with average health to 74 years of age.

Life expectancy

In select patients who are very healthy with an estimated life expectancy of at least ten years, ongoing screening every two to four years is reasonable following SDM as these patients are more likely to benefit from therapeutic interventions, if indicated. However, for patients with less than a ten-year estimated life expectancy, screening is not likely to provide a benefit in terms of disease-specific or overall mortality. The 95% confidence interval around the relative risk (RR) of prostate cancer mortality between the screening and control groups in ERSPC for patients aged 70 to 74 years excluded any benefit (RR: 1.18; 95% CI: 0.81 to 1.7).[75] Furthermore, the evidence from randomized treatment trials comparing surgery, radiation, and monitoring has shown to have less benefit and more risk from curative treatment with increasing age.[76-79] The risk in overdiagnosis of prostate cancer increases with increasing age.[58, 72, 80, 81] Estimates of overdiagnosis also depend on the study population, design, and estimation methodology.[82] Empirical estimates of overdiagnosis based on excess incidence from randomized screening trials are generally biased and overstate the long-term overdiagnosis risk.[82]

Risk calculators have been developed to estimate a patient's life expectancy and can be informative during SDM. While a number of methods have been applied for estimating life expectancy, a simple approach is to use the social security life tables (https://www.ssa.gov/oact/STATS/table4c6.html). Based on current Social Security Administration (SSA) data, American men older than 77 years of age have less than

a 10-year life expectancy. The Michigan Urological Surgery Improvement Collaborative (MUSIC) has deployed a paper-based life expectancy tool that includes comorbidities (e.g., https://musicurology.com/wp-content/uploads/2022/02/Hawken_et_al-2017-BJU_International.pdf). Insurance companies are known to be particularly astute at estimating life expectancy and many have online calculators that include the use of tobacco, alcohol, physical activities, and comorbidities. For the purpose of estimating life expectancy, the use of these tools is likely more reliable than individual clinician judgment.[83]

The Panel notes most studies regarding baseline PSA have been conducted in populations of primarily White patients. The Southern Community Cohort Study (100% Black patients) showed that PSA levels in midlife were similar to those among White controls in prior studies and were strongly associated with risk of aggressive prostate cancer.[66]

Given the limitations in the range of evidence supporting screening intervals and for discontinuing screening, use of SDM is recommended to assist clinicians in tailoring the decision to each patient. The Agency of Healthcare Research and Quality (AHRQ) has developed a simple approach for SDM that addresses common clinician and patient level barriers called the SHARE approach.[84] This approach recommends clinicians to **Seek** the patient's participation, **Help** patients explore and compare options, **Assess** the patient's values and preferences, **Reach** a decision together with the patient, and **Evaluate** the patient's decision. The use of publicly available decision aids may be helpful in SDM, where available, and are updated to the most current level of evidence.

8. **Clinicians may use DRE alongside PSA to establish risk of clinically significant prostate cancer. (*Conditional Recommendation; Evidence Level: Grade C*)**

The primary screening modality recommended for the early detection of prostate cancer is a PSA blood test. Clinicians should not use DRE as the sole screening method.

There is insufficient evidence to support adding DRE to PSA-based prostate cancer screening. The PPV of DRE as a screening method to detect prostate cancer is low. In the PROBASE trial, DRE was not effective for early detection; the PPV of a suspicious DRE at 50 years of age was 0.87% (as compared to 4.9% among patients aged 55 to 59 years in PLCO); of the 57 participants with suspicious DRE, 37 were biopsied and only 2 had prostate cancer (both GG1).[40]

For various reasons, clinicians may choose to complement PSA screening with DRE based on SDM; however, the evidence base for this practice is weak. In a U.S.-based cohort study, the risk for finding cancer among people with PSA < 4 ng/mL and abnormal DRE was only 3% but the addition of DRE was found to improve detection of higher-grade disease.[85] There are practical considerations for performing DRE in clinical practice, and it may not be acceptable to all patients as compared to a blood draw.

In contrast to a screening application, use of DRE subsequent to the screening encounter may be of value. It has been shown that the greatest utility of DRE in randomized trials is demonstrated in the workup of patients with an elevated PSA. For this reason, among patients with PSA ≥ 2 ng/mL, clinicians should strongly consider supplementary DRE to establish risk of clinically significant prostate cancer. In patients undergoing prostate biopsy for an elevated PSA during screening, abnormal DRE improves the PPV for any prostate cancer and GG2+ detection.[20, 86, 87] In ERSPC Rotterdam, the PPV of a suspicious DRE in conjunction with an elevated PSA level ≥ 3 ng/mL to detect prostate cancer was 48% compared to 22% in patients with a normal DRE. However, the impact of abnormal DRE on PPV became attenuated in the subsequent screening rounds.[86] In PLCO, the absolute difference in the risk of clinically significant prostate cancer at 10 years between patients with suspicious versus non-suspicious DRE was small for patients with PSA < 2 ng/mL (1.5% versus 0.7%), whereas the difference was modestly relevant for patients with PSAs 2 to 3 ng/mL (6.5% versus 3.5%) and clinically relevant for patients with PSA ≥ 3 ng/mL (23.0% versus 13.7%), all statistically significant increases.[88]

9. **For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy. (*Strong Recommendation; Evidence Level: Grade B*)**

With knowledge of a patient's age, PSA, DRE, percent free PSA, family history of prostate cancer, and presence

of a previous biopsy, large-scale studies in Europe and the U.S. have shown the addition of PSA velocity at various thresholds does not add value in predicting the presence of clinically significant prostate cancer.[89, 90] Therefore, PSA velocity should not be used as sole indication for secondary biomarker, imaging, or a biopsy. Paradoxically, very high PSA velocity (> 3 ng/mL/year) is more closely associated with the presence of inflammation on biopsy rather than cancer.[91]

10. Clinicians and patients may use validated risk calculators to inform the SDM process regarding prostate biopsy. (*Conditional Recommendation; Evidence Level: Grade B*)

Contemporary evaluations of prostate cancer risk now typically include patient demographic factors, medical history, family history of prostate cancer, biomarkers, and imaging findings. Simple nomograms in tabular format are suboptimal in presenting risk for more than a few such factors; therefore, several groups have developed risk calculators based on actual patient data that allow patients and clinicians to simultaneously incorporate a larger number of these risk factors. It is beyond the scope of this guideline to provide an exhaustive review of all published risk calculators, but several discussed by the Panel are listed below, noting that different risk calculators often use different risk factors.[92, 93]

One of the first risk calculators that was widely disseminated was based on the Prostate Cancer Prevention Trial (PCPT) nomogram.[94] A number of additional datasets and risk factors have since been incorporated.[95] This risk calculator currently includes race, age, PSA, percent free PSA, family history of prostate cancer, DRE, prior biopsy, and urinary PCA3. Chun is a comparable risk calculator that likewise includes age, PSA, DRE, prior biopsy, urinary PCA3, and prostate volume.[96] When compared, both of these risk calculators could be applied to estimate the risk of prostate cancer while also reducing the need for a prostate biopsy, although PCPT had higher AUC (0.84).[97] Several data-driven risk calculators developed based on a clinical trial were developed in Europe.[98] The ERSPC online tool has several applications ranging from a risk calculator for patients who are interested in screening but have not had a PSA, to a risk calculator that includes age, PSA, DRE, prior biopsy, and prostate volume.[99] More recently, prostate MRI was added to this calculator. When DeNunzio et al. compared PCPT, ERSPC and the Chun risk calculators, they found that Chun outperformed the other 2 when the endpoint was high-grade prostate cancer, defined as GG > 3 (Gleason Score ≥ 4+3=7);[100] however, they only utilized the PSA-only version of the ERSPC risk calculator. In 2018, the Prostate Biopsy Collaborative Group (PBCG) published their calculator based on age, PSA, DRE, Black ancestry, first-degree family history of prostate cancer, and prior negative biopsy.[101]

Table 4: Select Risk Calculators with Risk Factors and Risk Factors Evaluated

	PCPT V2 (https://riskcalc.org/PCPTRC/)	Chun (There is no publicly available online calculator for Chun)	ERSPC (https://www.prostatecancer-riskcalculator.com)	PBCG (https://riskcalc.org/PBCG/)
Race	x			x
Family history of prostate cancer	x			x
Age	x	x	x	x
PSA	x	x	x	x
Free PSA %	x	x		
DRE	x	x	x	x
Prior biopsy	x		x	x
Urinary PCA3	x	x		
TMPRSS2:ERG fusion	x			
Prostate volume		x	x	
Sampling density		x		
MRI – PI-RADS score			x	

Historically, clinicians have expressed concern that using risk calculators and nomograms are cumbersome and difficult to incorporate into practice; however, given the rise of Electronic Medical Records (EMR), and the use of computers in most clinical encounters, web-based risk calculators have become easily accessible for real-time clinical conversations. In the course of discussing prostate cancer risk, clinicians can easily enter pertinent risk information into their choice of risk calculator and produce estimates including likelihood of finding cancer, finding significant cancer, and often with graphics/icon arrays that aid in interpretation of individualized numerical risk data.

While these risk calculators provide estimates that facilitate clinician-patient discussion of detection risk, it should be kept in mind that these are population averages with potentially wide intervals in some subsets. Moreover, the data for a number of these, while extensive, may be based on historic screening and detection approaches (e.g., prior to widespread prostate MRI adoption). Furthermore, calibration of risk calculators may differ by subgroups. In one study, investigators compared PBCG with PCPT and concluded that PCPT performed better in minority groups.[92] One may also wish to use a U.S.-based risk calculator if this more closely resembles their practice population. Thus, clinicians need to incorporate their experience in the final refinement of risk estimates rather than solely relying on any of these risk calculator estimates as certainty.

11. **When the risk of clinically significant prostate cancer is sufficiently low based on available clinical, laboratory, and imaging data, clinicians and patients may forgo near-term prostate biopsy. (*Clinical Principle*)**

When assessing a patient's risk for prostate cancer, validated online calculators/nomograms may be used to incorporate multiple risk factors (e.g., PSA, family history of prostate cancer, race/ethnicity, age, DRE, percent free PSA, PSA density) to estimate risk of prostate cancer and risk of clinically significant prostate cancer.[102, 103] In many cases, the estimated risk for significant prostate cancer would be considered low as perceived by both the clinician and patient. Therefore, it would be reasonable to forgo a prostate biopsy in such instances following SDM, even where there may be some clinical features that indicate a risk for prostate cancer existing (e.g., mildly elevated PSA). If a decision is made after SDM to forgo a biopsy or additional testing, patients should be informed of their risk for underdiagnosing clinically significant prostate cancer and the need for future follow-up screening, as appropriate.

INITIAL BIOPSY

12. **Clinicians should inform patients undergoing a prostate biopsy that there is a risk of identifying a cancer, with a sufficiently low risk of mortality, that could safely be monitored with AS rather than treated. (*Clinical Principle*)**

A brief pre-biopsy discussion about pathologic findings warranting AS is expected to increase subsequent acceptance of AS by patients and lower rates of treatment. In a multicenter study of patients undergoing a prostate biopsy, GG1 prostate cancer was found in 44% and 61% of initial and repeat positive biopsies, respectively.[104] For low-risk prostate cancer, AS is the preferred management by the AUA and other international guidelines.[17] However, a statewide registry from Michigan has documented overtreatment among patients with low-risk prostate cancer and less than a 10-year life expectancy.[105] The primary intent of screening and surveillance is to identify higher-grade cancers that may prompt definitive treatment.

13. **Clinicians may use MRI prior to initial biopsy to increase the detection of GG2+ prostate cancer. (*Conditional Recommendation*; *Evidence Level: Grade B*)**

Studies have demonstrated the clinical value of mpMRI and using this to guide biopsy decision-making can increase the likelihood of detecting clinically significant prostate cancer while lowering detection of insignificant disease. This is particularly true in patients with a prior negative prostate biopsy; data from patients who are biopsy naïve are less definitive. The PRECISION trial (Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance or Not?) was a randomized non-inferiority study that sought to compare the effectiveness of MRI-targeted versus systematic biopsy in detecting clinically significant prostate cancer in biopsy-naïve patients.[106] This 500-patient trial was performed at 25 centers in 11 countries. mpMRI was performed with a 1.5T or 3T coil, and with or without an

endorectal coil. There was no central reading of the MRI prior to biopsy, and biopsies were performed by transrectal or transperineal route, using cognitive or ultrasound fusion technique. Hence, there was significant uncontrolled variability in reading of the MRI, method of biopsy, and fusion technique. Of patients who underwent an MRI, nearly 70% had a lesion targetable for biopsy (PI-RADS score ≥ 3). Clinically significant prostate cancer was detected in 38% of the patients undergoing mpMRI and 26% of patients undergoing systematic biopsy. Patients undergoing MRI targeted biopsy also had fewer insignificant cancers detected (9% versus 22%). The agreement between a local and a central read for MRI was 78%, which was considered moderate. Follow-up results in patients who had a negative MRI or negative MRI biopsy only are pending.

Other single center studies have compared effectiveness of pre-biopsy MRI with targeted and systematic biopsies to systematic biopsies alone in biopsy-naïve patients. The data from these studies are conflicting. Some studies reaffirm the findings of PRECISION in that an mpMRI driven biopsy strategy leads to higher detection of clinically significant prostate cancer while avoiding detection of insignificant disease.[107, 108] Other studies do not demonstrate a difference in either overall prostate cancer or clinically significant prostate cancer detection rates.[109, 110]

Prospective randomized studies that compared mpMRI-driven biopsy to standard systematic biopsy in biopsy-naïve patients, used varying reference standards such as radical prostatectomy findings or saturation biopsy findings to assess the accuracy of mpMRI.[108] Some do not list a reference standard.[109] Data on patients with no MRI-detected, biopsy-eligible lesions, are also not provided but these patients could subsequently be diagnosed with prostate cancer including clinically significant prostate cancer. Different techniques have been utilized to perform the MRI-guided biopsy such as cognitive versus image-guided fusion. Patients in the MRI arm have also undergone standard systematic biopsies in addition to MRI-guided biopsy. In some studies, those with negative MRI have crossed over to systematic biopsy.[107, 108] A more recent study by Hugosson et al. (2022) sought to examine the independent value of systematic biopsies in patients who had undergone an MRI following an elevated PSA. They found that avoidance of routine systematic biopsies and performing only MRI directed biopsies reduced the detection of clinically insignificant cancers. However, all individuals in this study underwent an MRI of the prostate and it did not address the question of need for routine MRI prior to biopsy. Patients with a PSA > 10 ng/mL and all patients with a diagnosis of cancer on MRI-guided biopsy, were offered systematic biopsies as well. Performance of systematic biopsies did result in detection of clinically significant prostate cancer (including a Gleason 3+5) which was missed on MRI-guided biopsy in a small subset of 10 people.[111]

Hence, while some data suggest the benefit of a pre-biopsy MRI in biopsy-naïve patients, conflicting reports moderate the enthusiasm for a strong recommendation. A Cochrane review on this topic pooled data from 18 studies that included biopsy-naïve patients and patients with prior negative prostate biopsy.[112] Analysis of the pooled data suggests the sensitivity of a pre-biopsy MRI is 0.91 (95% CI: 0.83 to 0.95), and specificity is 0.37 (95% CI: 0.29 to 0.46) for GG2+ prostate cancer. The pooled prostate cancer detection ratio for MRI prior to initial biopsy was 1.05 (95% CI: 0.95 to 1.16), which indicates prior MRI may have limited benefit in this setting. However, when considering patients who had undergone pre-biopsy MRI followed by a targeted and systematic biopsy compared to systematic biopsy alone, the pooled analysis found an additional 10 patients (out of 100 biopsied) would be diagnosed with clinically significant prostate cancer. The reference standard utilized for this analysis was detection of clinically significant cancer on template biopsy. The study found there to be significant heterogeneity in study conduct as well as high risk of bias in sample selection and reference standard. Hence, the study authors graded the evidence as low.

In anticipation of more definitive data, it is reasonable to obtain an mpMRI in biopsy-naïve patients prior to their first biopsy, but such a practice cannot be regarded as the standard approach based on the currently available evidence. As in the PSA screening setting, the use of SDM is highly recommended given the uncertainty involved.

14. Radiologists should utilize PI-RADS in the reporting of mpMRI imaging. (*Moderate Recommendation; Evidence Level: Grade C*)

Since the development of the first version of PI-RADS in 2012[113] with subsequent versions in 2015 (v2.0)[114] and

2019 (v2.1),[115] the system has been widely adopted and has standardized the reporting of mpMRI. Multiple studies have confirmed PI-RADS score, either on a per lesion or per patient basis, correlates with likelihood of detecting any cancer and GG2+ cancer. Table 5 summarizes the detection prevalence for any prostate cancer and GG2+ prostate cancer based on the PI-RADS score when 23 studies[116-138] identified by the systematic review were pooled. Of the 23 studies, 10 reported on a per lesion analysis[117, 119, 120, 122, 124, 125, 128, 129, 133, 136] and 13 reported on a per patient analysis using an index lesion.[116, 118, 121, 123, 126, 127, 130-132, 134, 135, 137, 138] While PI-RADS v2.1 provides a structured system for lesion-based scoring approach and has contributed to the wider use of prostate MRI over the last decade, some of the required evaluation criteria remain subjective. As a result, reader variability remains a challenge,[136] especially for novice readers.[139] Reported measures of interobserver agreement for PI-RADS v2.1 include a weighted kappa value of 0.700 for a study with 5 radiologists of varying experience[140] and a Conger kappa value of 0.64 for a study with 6 radiologists of varying experience.[141] While interpretative variability remains a limitation, there is evidence that agreement is greater for PI-RADS v2.1 compared to v2.0 and also greater for more experienced readers.[142] Reader variability is only one of multiple factors that may influence performance differences between sites, including heterogeneity in patient selection, technical factors (e.g., MRI manufacturer and field strength, and use of an endorectal coil), method of prostate biopsy used for pathological correlation, and pathologist expertise and variability. Minimum training requirements to establish reader experience have been proposed and are under investigation.[143, 144] Continued evolution of training criteria and further iterative refinements of the PI-RADS should result in greater accuracy and reader agreement. In the interim, clinicians should interpret PI-RADS scores in the context of known local experience and expertise. This statement applies to both initial and repeat biopsy situations.

Table 5: Prevalence of Prostate Cancer Detection based on PI-RADS Score*

PI-RADS Score	Any Prostate Cancer (% (95%CI))	Clinically Significant Prostate Cancer (% (95%CI))
1 or 2	15% (95%CI: 8% to 22%)	7% (95%CI: 4% to 11%)
3	25% (95%CI: 22% to 29%)	11% (95%CI: 8% to 14%)
4	58% (95%CI: 53% to 63%)	37% (95%CI: 33% to 40%)
5	85% (95%CI: 80% to 90%)	70% (95%CI: 62% to 79%)

*Detection prevalence for both any prostate cancer and clinically significant prostate cancer based on the PI-RADS score when 23 identified studies were pooled using a random-effects inverse-variance method.[116-138] Due to the paucity of data using only PI-RADS version 2.1, pooled studies used version 1.0 through version 2.1.

15. **For biopsy-naïve patients who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy. (*Moderate Recommendation [targeted biopsies]/Conditional Recommendation [systematic template biopsy]; Evidence Level: Grade C*)**

In the setting where a prostate MRI identifies a lesion suspicious for cancer (e.g., PI-RADS 3 to 5) among patients who are biopsy-naïve, clinicians will be confronted with a decision to proceed with targeted biopsies along with systematic biopsies, or to proceed with targeted biopsies alone. A number of observational studies have shown a higher detection of clinically significant prostate cancer when both targeted and systematic biopsies are combined.[119, 121, 145-150] In a study of 300 patients with either a PSA ≥ 4 ng/mL or an abnormal DRE, fusion biopsy detected 69%, systematic 12-core biopsy detected 80%, and combination of both yielded 87% of all GG2+ tumors.[146] These and other studies are further supported by a larger study that included a mix of biopsy-naïve patients and patients with prior biopsies. In this study of over 400 biopsy-naïve patients, a combination of targeted and systematic biopsies resulted in 9.9% greater detection of cancer than either approach alone.[151] Further, this study noted that the combination approach resulted in the lowest rate of surgical upgrading (3.5%) in a subset of patients who underwent prostatectomy .[151] It has been hypothesized that systematic biopsies may improve detection of GG2+ cancer in some cases by sampling the target when the targeted cores may have missed the target.[152, 153] Systematic biopsy alone detected 1.9% high-grade cancers (defined as GG3 or higher) that MRI-targeted biopsy failed to detect. In a post hoc analysis of this study, an expert genitourinary radiologist reviewed all the prostate MRIs and tracked the systematic and MRI targeted biopsy cores from these 41 patients. The registration targeting error during the MRI-ultrasound fusion biopsy accounted for 51% of the misses, with MRI invisible lesions or missed MRI lesions by radiology accounting for the remainder.[154] While not widely available, use of an in-bore biopsy approach eliminates the co-registration error but does not allow for systematic biopsy.[155] In contrast, Kim et al. found little difference in detection between the combined approach and targeted cores.[149] In reviewing the literature, the Panel found published studies have used a variety of fusion platforms, biopsy approaches, and systematic templates, making direct comparison prohibitive. In most cases an indication for a fusion biopsy was PI-RADS 3 to 5 findings on MRI. The tradeoff for finding more GG2+ cancer, with adding a systematic biopsy to the target only approach, is that more GG1 cancer will also be diagnosed. In recent publications, this rate has been reported between 1.2% and 5% GG1.[111, 151] Following the literature review window for these guidelines, a randomized trial comparing targeted biopsy alone versus targeted plus systematic biopsies among patients with PI-RADS 3 to 5 findings on MRI was published.[111] This study demonstrated a 50% reduction in detection of GG1 cancers (absolute reduction from 1.2% to 0.6%), and a 27% reduction in findings of GG2+ cancers (absolute reduction from 1.1% to 0.8%), in the target-only arm. Although the decreased detection of GG2+ cancer detection was not statistically significant, (the study was not powered to detect this difference) it may well be clinically significant.[111] As in the PSA screening setting, use of SDM is highly recommended given the uncertainty involved.

16. **For patients with both an absence of suspicious findings on MRI and an elevated risk for GG2+ prostate cancer, clinicians should proceed with a systematic biopsy. (*Moderate Recommendation; Evidence Level: Grade C*)**

In a systematic review of 42 studies, the negative predictive value (NPV) of a "negative" MRI (defined as PI-RADS 1 to 2) to detect GG2+ prostate cancer among biopsy-naïve patients was 91%.[156] Thus, approximately 1 in 10 patients who have a negative prostate MRI may have GG2+ cancer on biopsy, although rates widely vary by study and the risk factors of the individual person. If the definition of a "negative" MRI was expanded to include PI-RADS 3, then NPV decreased to 87%.[156] Multiple factors contribute to risk calculation, including race, age, total PSA, PSA density, percent free PSA, and family history of prostate cancer, as used in available risk calculators. Therefore, patients with elevated risk for GG2+ prostate cancer and absence of findings on MRI should proceed with a systematic biopsy. A systematic biopsy should include a minimum of 12 cores, distributed throughout the prostate, with thorough sampling of the peripheral zone. Various templates employing these principles exist for transrectal and transperineal approaches.[157-160] If a decision is made after SDM to omit a systematic biopsy,

patients should be informed of their risk for underdiagnosing clinically significant prostate cancer.

17. **Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (*Conditional Recommendation*; *Evidence Level: Grade C*)**

There are several blood and urine markers available alone or in combination to further risk stratify patients with a mildly elevated PSA, typically between 2.5 and 10 ng/mL. The intent is to improve upon the poor specificity of PSA and avoid the risks associated with unnecessary biopsies, including the risk of overdiagnosis of GG1 prostate cancer, in patients with a low probability of harboring GG2+ disease. Naturally, with avoidance of biopsies comes the risk of delaying the diagnosis of clinically significant prostate cancer ("false negatives"). Tests that report the likelihood of any prostate cancer, rather than reporting GG2+ prostate cancer are less valuable in terms of ameliorating overdiagnosis of low-grade prostate cancer.

Importantly, such biomarkers should not be used in situations in which, based on available clinical and laboratory data, the risk of GG2+ prostate cancer is so low or so high the result of adjunctive biomarkers would not influence the decision of whether to proceed with further testing (e.g., MRI and/or biopsy). For example, in patients with a prostate nodule, a PSA > 10 ng/mL, a strong family history of high-grade prostate cancer, or other significant risk factors, it is unlikely an adjunctive biomarker would change the decision to proceed with biopsy. In contrast, in a patient with a mildly elevated PSA, a very low PSA density (based on available imaging-based volume measurement), no other risk factors, and a desire to avoid biopsy, ongoing screening rather than further testing is preferable.

Perhaps the most widely available adjunctive test is percent free PSA. Lower percent free PSA is associated with greater likelihood of identifying prostate cancer on biopsy.[161-166] Additionally, it improves upon the prediction of GG2+, primarily in validation studies of multiplex tests that include percent free PSA. For example, in the study validating the use of the 4Kscore™, exclusion of percent free PSA from the model reduced the AUC from 0.821 (95% CI: 0.790 to 0.852) to 0.699 (95% CI: 0.664 to 0.735).[167] Similarly, percent free PSA improves prediction of GG2+ prostate cancer compared to total PSA (AUC 0.661 versus 0.551) in a study demonstrating the value of prostate health index (PHI)™.[168]

Numerous studies have shown that higher PSA density (serum PSA [ng/mL] divided by imaging measures of prostate volume [cc]) is associated with the risk of identifying clinically significant prostate cancer on biopsy.[169-171] Various thresholds have been proposed, with lower thresholds (e.g., PSA density $\geq$ 0.07) having higher sensitivity, but lower specificity, than higher thresholds (e.g., PSA density $\geq$ 0.15). Thus, PSA density is an important component of disease risk assessment when imaging is available for volume measurement. However, the Panel recognizes the continuous nature of risk associated with the spectrum of PSA density values and cautions against use of threshold values in isolation for management decision-making.

It is debatable which of the newer biomarkers (alone or in combination) is best, and comparative studies are sparse. A table of available tests for an initial biopsy cohort is summarized (**Table 6**). In general, the tests are calibrated such that avoiding biopsy in the setting of a sub-threshold test reduces biopsies by about one third, resulting in delayed detection or non-detection of 5% to 10% of clinically significant prostate cancers.[172] A meta-analysis of studies that met criteria for inclusion in the evidence base for this guideline showed that use of secondary biomarkers would reduce the number of biopsies by 35% (95% CI: 26% to 44%; p<0.0001),[169, 173-184] and 9% (95% CI: 6% to 11%; p<0.0001)[169, 171, 173-178, 180-182, 185] of clinically significant prostate cancers would not be detected. A modeling study evaluating several of the tests in the reflex setting (to refer patients with PSA between 4 to 10 ng/mL to biopsy at pre-specified cutoffs) projected that if patients were screened annually the tests would minimally impact life years or quality-adjusted life years compared with all patients with PSA > 4 ng/mL undergoing biopsy.[186] Given their generally significant impact on biopsy reduction and their projected minimal impact on life expectancy, such tests may be of value among patients with modestly elevated PSA tests, especially in patients with a prior negative biopsy in whom PSA alone is not recommended as the sole trigger for re-biopsy. Considerations in selecting a test include test performance characteristics (such as NPV), availability, and familiarity. As in the PSA screening setting, the use of SDM is highly recommended given the uncertainty

involved. This statement applies to both initial and repeat biopsy situations.

Table 6: Available Biomarker Assays

Test	Biomarker Component	Clinical Variable	Biopsy Population
Serum			
4Kscore[175, 183, 187, 188]	PSA, fPSA, iPSA, hK2	Age, prior biopsy status, DRE (optional)	Initial biopsy[175, 183, 187] Repeat biopsy[188]
IsoPSA*[189]	All PSA isoforms	None	Not specified[189]
Proclarix[190]	THBS1, CTSD, PSA, fPSA	Age, prostate volume (optional)	Mixed[190]
PHI[169-171, 173, 183, 191-193]	p2PSA, fPSA, PSA	None	Initial biopsy[169-171, 173, 183] Repeat biopsy[191-193]
STHLM-3[20, 22, 25]	232 genetic polymorphisms (SNPs), PSA, fPSA, iPSA, hK2, MSMB, MIC1	Age, family history, previous biopsy, DRE (optional)	Mixed[20, 25]
Post-DRE Urine			
PCA3[170, 174, 176, 185, 194-197]	PCA3	Some studies add age, PSA, prostate volume	Initial biopsy[170, 174, 176, 185, 194, 195] Repeat biopsy[196, 197]
MPS[179, 195, 198, 199]	PCA3, TMPRSS2:ERG, PSA	None	Initial biopsy[179, 195, 198, 199] Repeat biopsy[198]
SelectMDx[180, 200]	HOXC6, DLX1 mRNA	Age, PSA, prostate volume, DRE	Initial biopsy[180, 200]
TMPRSS2:ERG[195]	TMPRSS2:ERG	None	Initial biopsy[195]
Urine			
ExoDx Prostate Intelliscore[181, 182, 184, 201]	PCA3, ERG, SPDEF mRNA	None	Initial biopsy[181, 182, 184] Repeat biopsy[201]
MiR Sentinel[202]	Small non-coding RNAs	None	Mixed[202]
Tissue			
Confirm MDx[203, 204]	Hypermethylation of GSTP1, APC, RASSF1	None	Repeat biopsy[203, 204]

(Abbreviations: DRE, digital rectal exam; fPSA, free PSA; iPSA, intact PSA; mRNA, messenger ribonucleic acid; PSA, prostate-specific antigen; SNP, single nucleotide polymorphism.)
*IsoPSA was not included in the initial literature search based on its infrequent use; however, it was identified on a secondary targeted search and included here for completeness.

18. **For patients with a PSA > 50 ng/mL and no clinical concerns for infection or other cause for increased PSA (e.g., recent prostate instrumentation), clinicians may omit a prostate biopsy in cases where biopsy poses significant risk or where the need for prostate cancer treatment is urgent (e.g., impending spinal cord compression). (*Expert Opinion*)**

For patients with a PSA > 50 ng/mL and no evidence of inflammation, infection, recent instrumentation or catheterization, the likelihood of high-grade prostate cancer has been estimated to be as high as 98.5%.[205] Therefore, in situations where biopsy may be risky (e.g., anticoagulation, significant comorbidity, frailty) or delay urgent treatment (e.g., spinal cord compromise from metastases), immediate biopsy can be delayed or omitted. The extremely high risk of prostate cancer should be shared with the patient, and SDM should be used in the decision on whether to omit an immediate prostate biopsy. This recommendation does not exclude the potential to proceed with biopsy or other prostate cancer evaluation, if deemed clinically appropriate. In addition, it does not obviate the need for biopsy at a later time (e.g., required for treatment, insurance, genetic testing). Imaging to establish extent of disease or confirm metastasis may be helpful if an immediate biopsy is not performed.

REPEAT BIOPSY

19. **Clinicians should communicate with patients following biopsy to review biopsy results, reassess risk of undetected or future development of GG2+ disease, and mutually decide whether to discontinue screening, continue screening, or perform adjunctive testing for early reassessment of risk. (*Clinical Principle*)**

20. **Clinicians should not discontinue prostate cancer screening based solely on a negative prostate biopsy. (*Strong Recommendation; Evidence Level: Grade C*)**

21. **After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy. (*Strong Recommendation; Evidence Level: Grade B*)**

22. **If the clinician and patient decide to continue screening after a negative biopsy, clinicians should re-evaluate the patient within the normal screening interval (two to four years) or sooner, depending on risk of clinically significant prostate cancer and life expectancy. (*Clinical Principle*)**

23. **At the time of re-evaluation after negative biopsy, clinicians should use a risk assessment tool that incorporates the protective effect of prior negative biopsy. (*Strong Recommendation; Evidence Level: Grade B*)**

Following a prostate biopsy, clinicians should not only share biopsy results with patients but also make recommendations for further follow-up. Routine management after a negative biopsy would be resumption of screening. The time frame for next evaluation should mirror the standard screening interval, such that a patient should be re-evaluated within two to four years or sooner, typically with a PSA (see statement 6).

While negative prostate biopsy significantly lowers the probability of subsequently identifying GG2+ prostate cancer, the protective effect of a negative biopsy likely subsides over time since prior biopsy. Patients with a prior negative biopsy remain at risk for undetected or subsequent development of GG2+ disease. The systematic review performed for this guideline, has shown that 5% to 25% of patients who undergo a subsequent biopsy in the short term are diagnosed with GG2+ disease.[206-214] Additionally, over a 20-year time horizon, the risk of prostate cancer mortality ranges from 1.4% to 5.2%.[215, 216] Therefore, a negative biopsy alone should not be used to justify discontinuation of prostate cancer screening.

PSA level alone should not be used to decide whether to repeat the prostate biopsy in patients with a previous negative biopsy.[101] While PSA does factor into risk calculation, it should not be used exclusively to justify repeat biopsy, especially if the original biopsy was prompted by an elevated PSA, because this can result in repeated unnecessary biopsies. If concern remains elevated for GG2+ based on PSA density, previous MRI findings, or other factors, the clinician and patient may consider adjunctive testing (blood, urine, or tissue tests), or MRI (if not previously performed) to further risk stratify the patient and guide further management.

The likelihood of identifying GG2+ disease on subsequent biopsy has been associated with a few factors, including age, Black ancestry, total PSA, percent free PSA,[102] PSA density,[217] abnormal DRE findings, presence of germline mutations, pathology findings on prior biopsy (e.g., AIP), results of available adjunctive testing, number of cores taken at initial biopsy, MRI findings, planned method of subsequent biopsy (e.g., number of cores, saturation, template mapping),[206-214] and family history.[101] Previous biopsy reduces the risk of identifying GG2+ disease on subsequent biopsy and should be considered in decisions about further management.[101]

Given the multiple factors involved in computing the risk of GG2+ disease, the Panel recommends use of a risk calculator (see statement 10) that incorporates standard factors, with or without additional factors.[101, 102, 217, 218] (**see Table 4**)

For example, in a patient with a low risk of GG2+ disease based on risk calculation, the clinician and patient may decide to discontinue further prostate cancer screening (see statement 7). Although, in a standard/high-risk patient, the clinician and patient may resume interval screening with or without adjunctive testing and/or repeat biopsy. As in the PSA screening setting, the use of SDM is highly recommended given the uncertainty involved.

24. After a negative initial biopsy in patients with low probability for harboring GG2+ prostate cancer, clinicians should not reflexively perform biomarker testing. (*Clinical Principle*)

The goal of early detection is to identify patients at high risk for harboring GG2+ prostate cancer. While biomarkers may improve the capacity to identify patients at risk for high-grade disease, these tests generally provide the probability of disease or high-grade disease as discussed previously (statement 17). In patients with a negative biopsy, with low probability for GG2+ disease, it is unlikely that additional biomarker tests will be informative. For example, a low PSAD (≤ 0.10 ng/mL^2) at the time of initial prostate biopsy is associated with a low likelihood of harboring GG2+, including in the setting of negative or equivocal mpMRI.[219, 220] It is unlikely a biomarker test will provide any additional clinically actionable information in this scenario. Thus, clinicians should not implement reflex biomarker testing without prior consideration to the utility of the test or how the information gathered will impact the decision to undergo repeat biopsy.

25. After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. (*Conditional Recommendation; Evidence Level: Grade C*)

Blood, urine, or tissue-based biomarkers may provide additional information for risk stratification in patients with a prior negative biopsy and with ongoing suspicion for GG2+ prostate cancer. Several blood (e.g., PHI, 4Kscore, PSAD),[188, 191, 219, 220] urine (e.g., ExoDx, SelectMDx, MPS, PCA3), and tissue-based (e.g., ConfirmMDx)[221, 222] biomarkers have been developed and reported in several studies with varying performance characteristics. These tests generally present percentage risk of biopsy-detectable disease (and/or GG2+), and it is up to the clinician and patient to decide on the threshold for proceeding with a biopsy with consideration given to the performance metrics of the test. For example, the proportion of GG2+ prostate cancer missed by 4Kscore at ≥ 10%, 15%, and 20% threshold were 5%, 16%, and 16%, respectively, which might impact a patient's decision to pursue a repeat prostate biopsy.[188] Additionally, there is significant heterogeneity in the outcomes reported for these biomarkers. For example, ConfirmMDx, the only tissue-based biomarker assessing epigenetic changes in *GSTP1, APC, RASSF1* in negative biopsy tissue was developed in the MATLOC study[221] and validated in the DOCUMENT[222] study to detect any prostate cancer and not specifically for GG2+ disease. Moreover, how to integrate the use of these tests with mpMRI in prostate cancer early detection paradigms is yet to be studied comprehensively.[192, 193, 223] In a study, combining mpMRI with PHI improved the NPV of mpMRI from 78% to 95% and AUC from 0.64 to 0.75 for detecting GG2+ cancer.[192] In a recent study, MPS was shown to be significantly associated with GG2+ cancer across all PI-RADS scores inclusive of PI-RADS 3 lesions.[223] Pending future prospective validation studies, biomarkers may augment mpMRI for identifying patients for prostate biopsy especially in patients with negative or equivocal mpMRI findings but with ongoing suspicion for GG2+ cancer. It is imperative clinicians are familiar with biomarkers, understand what information or data each test provides,

and consider whether additional information will impact management decisions before ordering a test. As in the PSA screening setting, the use of SDM is highly recommended given the uncertainty involved.

26. In patients with focal (one core) HGPIN on biopsy, clinicians should not perform immediate repeat biopsy. (*Moderate Recommendation; Evidence Level: Grade C*)

The risk of cancer detection following a diagnosis of HGPIN has evolved. Early reports that utilized less than 12-core systematic sampling often found a high risk of undetected prostate cancer.[224, 225] However, contemporary studies indicate a 20% to 30% risk of any cancer detected (not just high-grade) in subsequent biopsies,[214, 226-232] which is the same risk following an initial benign biopsy. Even when repeat biopsy is performed, the risk of GG2+ carcinoma is relatively low (~10%).[226, 228, 229, 231, 232] As such, immediate repeat biopsy is not recommended for patients with a diagnosis of focal HGPIN on initial biopsy.[233] Nonetheless, routine follow up is warranted, which may include mpMRI and/or additional biomarkers (see statements 25 and 30). Patients with a diagnosis of HGPIN in the setting of other biopsy cores showing invasive prostate cancer should be managed in accordance with the definitive carcinoma component.

27. In patients with multifocal HGPIN, clinicians may proceed with additional risk evaluation, guided by PSA/DRE and mpMRI findings. (*Expert Opinion*)

Relatively few studies on the risk of prostate cancer following an initial diagnosis of HGPIN have focused on multifocal HGPIN (e.g., HGPIN in $\geq$ 2 cores). Older reports suggest a higher risk of cancer detection for multifocal HGPIN (approximately 30% to 45%), compared to isolated HGPIN.[214, 226, 234] However, these studies lacked repeat biopsy with mpMRI and did not specify the detection of clinically significant prostate cancer. More recent data with repeat biopsy done with mpMRI guidance demonstrate that in approximately 25% of patients with previous multifocal HGPIN, serum PSA and/or DRE are normalized after the non-cancer bearing prostate biopsy.[235] The risk of GG2+ detection in repeat biopsies of patients with multifocal HGPIN is approximately 30%, which is not higher than in those without this finding.[235] In patients with persistent prostate cancer suspicion, the risk of detecting clinically significant prostate cancer in repeat prostate biopsies, based on PSA and DRE, is independent of the previous finding of HGPIN. Thus, a recommendation to repeat a prostate biopsy after HGPIN should be based on PSA and DRE evolution, and mpMRI findings. Due to a lack of data stating otherwise, repeat prostate biopsy should not be recommended solely because of a previous diagnosis of HGPIN, even if multifocal. As in the PSA screening setting, the use of SDM is highly recommended given the uncertainty involved.

28. In patients with ASAP, clinicians should perform additional testing. (*Expert Opinion*)

29. In patients with AIP, clinicians should perform additional testing. (*Expert Opinion*)

In routine pathology reports, ASAP is synonymous with a small focus (or foci) of atypical glands suspicious, but not definitive, for a diagnosis of carcinoma.[236-238] An ASAP finding alone on needle biopsy is associated with a 30% to 50% risk of prostate cancer detection on repeat biopsy,[214, 225, 229, 233, 236-243] with approximately 10% to 20% of these being GG2+.[225, 241-243] Less information is available on the risk of prostate cancer detection following an ASAP diagnosis in patients for whom MRI-targeted biopsy was included in the initial biopsy. Given these risks, additional testing should be considered following an ASAP diagnosis, which may include repeat systematic needle biopsy with consideration of mpMRI +/- targeted biopsy, PSA, as well as urine, or serum biomarkers (see statements 25 and 30). Patients with a diagnosis of ASAP in the setting of other biopsy cores showing invasive prostate cancer should be managed in accordance with the definitive carcinoma component.

AIP describes lesions with greater architectural complexity and/or cytologic atypia than would be expected in HGPIN but lacking definitive criteria for the diagnosis of intraductal carcinoma (IDC-P).[244-248] AIP encompasses many of the lesions formerly designated cribriform HGPIN, exhibiting loose cribriform architecture with moderate cytologic atypia, but lacking marked pleomorphism or necrosis.[244, 245] AIP, like IDC-P, is usually seen in the context of GG2+ cancer, but uncommonly, may be seen as a sole finding on biopsy or in association with GG1 cancer only. Although there are no prospective studies or those with extended follow-up, available data suggest a close association with unsampled IDC-P[246, 248] and similar adverse pathologic characteristics as IDC-P in patients who went onto radical

prostatectomy.[247, 248] Given these associations, a diagnosis of AIP as either the sole finding or together with GG1 cancer only warrants additional testing, which may include early repeat systematic needle biopsy or MRI +/- targeted biopsy. The timing of additional testing should be based on reassessment of risk and SDM. Patients with a diagnosis of AIP in the setting of other biopsy cores showing clinically significant prostate cancer should be managed in accordance with the definitive carcinoma component. As in the PSA screening setting, the use of SDM is highly recommended given the uncertainty involved.

30. **In patients undergoing repeat biopsy with no prior prostate MRI, clinicians should obtain a prostate MRI prior to biopsy. (*Strong Recommendation; Evidence Level: Grade C*)**

Repeat biopsy is generally performed when there remains ongoing concern for GG2+ prostate cancer. One role for an MRI is to evaluate for suspicious lesions for targeted biopsy that may have been missed on a prior biopsy. In patients with a prior negative systematic biopsy, MRI will show a suspicious target (variably defined) in 36% to 90% of patients and a biopsy directed to the target will be positive in 37% to 66% of patients,[249-253] and positive for GG2+ cancer in 21% to 60% of patients.[250, 252, 253] In patients with a prior biopsy showing only GG1 disease, MRI will show a suspicious target (variably defined) in 33% to 51% of patients and a biopsy directed to the target will be positive for GG2+ disease in 49% to 90% of patients.[147, 253-255] Given the substantial rates of suspicious target identification and PPV for GG2+ disease in the repeat biopsy setting, an mpMRI is recommended if there was no prior imaging.

31. **In patients with indications for a repeat biopsy who do not have a suspicious lesion on MRI, clinicians may proceed with a systematic biopsy. (*Conditional Recommendation; Evidence Level: Grade B*)**

Repeat biopsy should be used judiciously after an initial negative biopsy, as repeat biopsy detects fewer and less lethal cancers. Medicare data show 38% of patients with an initial negative biopsy of the prostate undergo a repeat biopsy within 5 years, and the percentage of positive biopsies falls from 34% for the first biopsy to 25% for the second.[256] Nevertheless, many patients have indications for repeat biopsy. Factors that may identify patients likely to have clinically significant prostate cancer after a negative biopsy and a negative MRI include a PSA density > 0.15 ng/mL,[257] a PHI density value > 0.44,[258] or a PSA velocity of 0.27 ng/mL/year or greater.[259] MRI can be an important factor in the decision to perform a repeat biopsy, although a meta-analysis of 29 eligible studies with 8,503 participants[260] suggested mpMRI misses 13% of all cancers. Thus, if a patient has sufficient risk of GG2+ cancer with a negative prostate MRI, clinicians may proceed with systematic biopsy.

32. **In patients undergoing repeat biopsy and who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy. (*Moderate Recommendation [targeted biopsies]/Conditional Recommendation [systematic template biopsy]; Evidence Level: Grade C)***

In the repeat biopsy setting with targeted and systematic biopsy, the frequency of cancer found in systematic biopsy samples range from 5% to 10% across multiple studies.[151, 261, 262] While these results suggest a combined biopsy with systematic and targeted cores optimizes cancer yield, such an approach entails obtaining a larger number of cores, which may increase patient discomfort and other biopsy-associated complications,[263, 264] and the apparent incremental yield of off-target biopsy samples may be influenced by the sampling error associated with software image registration at targeted biopsy.[265] Ultimately, the decision to perform systematic sampling in addition to target sampling should be based on an integrated evaluation of MRI factors such as quality and confidence in target presence and clinical factors such as PSA, technique of initial biopsy, and time since prior systematic biopsy.

BIOPSY TECHNIQUE

33. **Clinicians may use software registration of MRI and ultrasound images during fusion biopsy, when available. (*Expert Opinion*)**

Targeted prostate biopsy of a visible lesion on mpMRI can be performed using software-based registration of mpMRI images and real-time ultrasound or cognitive registration. Other than in 1 RCT[266] where software-based registration demonstrated better cancer detection rate (CDR)

compared with cognitive registration (33.3% versus 19.0%; p=0.016), both approaches have been shown to have similar CDR in multiple studies,[267-270] inclusive of an RCT showing no difference in CDR of software-based versus cognitive fusion or in-bore MRI targeted biopsy.[271] Nonetheless, use of software registration facilitates the fusion of multiple MRI and ultrasound images in two to three planes, allowing for the creation of a composite image that provides a more comprehensive view of the target lesion. Thus, clinicians with relevant training and experience may use software-based registration of mpMRI and ultrasound images during fusion biopsy, when available, especially for small MRI lesions. There are drawbacks, however, to implementing software-based fusion biopsy program. There are technical issues (e.g., software bugs, system crashes), operator error, and unusual anatomy (e.g., large prostates, previous transurethral resections of the prostate). Thus, the ability to perform cognitive fusion techniques using anatomic fiducial markers such as intraprostatic cysts may augment software-based fusion approaches in some cases such as to minimize the risk of misregistration. Clinicians who adopt the cognitive fusion technique exclusively should undergo advanced training in MRI interpretation to optimize cancer detection.

34. Clinicians should obtain at least two needle biopsy cores per target in patients with suspicious prostate lesion(s) on MRI. (*Moderate Recommendation; Evidence Level: Grade C*)

The optimal number of biopsy cores per MRI target may differ based on multiple factors including patient characteristics (e.g., age, PSA, biopsy naïve versus prior biopsy), target characteristics (e.g., size, location, PI-RADS classification), and biopsy approach/technique (e.g., software fusion versus cognitive fusion, transrectal versus transperineal).[272] In general, higher number of biopsy cores per target improves the CDR at the potential expense of increased complication rate and time.[273] However, the incremental value in cancer detection is diminished after obtaining more than three cores per target.[273, 274] In patients with a suspicious prostate lesion(s) by MR imaging, at least two needle cores per target provides the most reproducible and accurate cancer detection rate. For prostate cancer risk group stratification, all cores from the same MRI target should be considered as a single core.[275]

35. Clinicians may use either a transrectal or transperineal biopsy route when performing a biopsy. (*Conditional Recommendation; Evidence Level: Grade C*)

In patients with a suspicion for GG2+ prostate cancer who are undergoing biopsy, the CDRs associated with transrectal versus transperineal biopsy route are not significantly different.[158, 276] There is some suggestion that transperineal biopsy may detect anterior and apical cancers at a higher rate; however prospective, randomized data are lacking and existing data are contradictory.[277] Recent meta-analyses and retrospective reviews of single center data suggest a lower risk of infection with the transperineal approach; however, prospective, randomized data are lacking to make a definitive conclusion.[277-280] Use of transperineal biopsies may have some value in patients who have experienced infectious complications with a prior biopsy, are at higher risk for biopsy-related infection, or have anterior lesions that may not be as easily accessible transrectally. There are at least two RCTs listed in clinicaltrials.gov that address this question (https://clinicaltrials.gov/ct2/show/NCT04815876 and

https://clinicaltrials.gov/ct2/show/NCT05179694) and the results are pending. Given the concern surrounding the rising rate of sepsis and antibiotic resistance, using transperineal biopsy to mitigate these concerns is a reasonable approach and is gaining traction. On the other hand, use of transrectal approach may be appropriate in certain situations (e.g., patient preference/comfort, patient cannot be placed into the lithotomy position, clinician training/experience or lack of appropriate equipment for the transperineal approach). Moreover, use of adjunctive measures (e.g., rectal swab cultures, augmented antibiotic approaches) to reduce sepsis for a transrectal biopsy approach have also been shown to reduce sepsis in a large statewide registry consisting of 30 practices.[281, 282]

Future Directions

Screening and diagnosis of prostate cancer remain intensely debated topics with major implications for individual and population health. There continue to be many unanswered questions that can prompt future research, preferably in the form of clinical trials and modeling studies to enhance and optimize patient care. Future trials will hopefully prioritize inclusion of historically underrepresented populations.

SDM regarding whether to screen, how frequently, and when to proceed to secondary testing (e.g., imaging or biomarkers) or biopsy is critically important. However, clinicians tend to discuss potential benefits of screening far more frequently than potential harms.[283] There is an unmet need for decision aids in multiple languages for persons at various levels of health literacy which clearly and comprehensively inform the patient of potential benefits and harms.

For populations at higher risk of being diagnosed with prostate cancer, such as those with a concerning family history of prostate cancer, Black ancestry, genetic risk, or elevated baseline PSA, a targeted and perhaps more intensive screening warrants further investigation. Additionally, investigation of novel approaches is strongly encouraged which may have operating characteristics which outperform currently available tools. Conversely, to minimize overdetection rates, people with a very low likelihood of clinically significant prostate cancer may benefit from less intensive or discontinuation of screening.

Although emerging data exist, a far more comprehensive understanding is required of the impact of race and ethnicity on the operating characteristics of PSA, secondary biomarkers, and prostate imaging. It is also essential to recognize many people undergoing screening are of mixed (or unknown) race and ethnicity. Since dramatic disparities exist regarding access and affordability of certain diagnostic or imaging modalities, efforts should be made by clinicians, payors, and health care systems to bridge this gap.

For non-binary patients or transgender women there is a lack of data on prostate cancer screening preferences, if and when to initiate, the accuracy of biomarkers (e.g., PSA, secondary biomarkers, MRI), potential psychological consequences, impact of gender-affirming hormonal therapy, and priorities regarding management options.[284] Considerably more effort and research are required.

While there are a plethora of serum, urine, tissue, and imaging biomarkers to assess the likelihood of high-grade prostate cancer, there is little knowledge on comparative effectiveness, how they may complement or supplement each other, and how various stepwise algorithms perform. Considerable research is required to achieve the goal of a highly effective, practical, scalable, and widely available approach.

Use of transperineal versus transrectal biopsy varies widely by country and within regions of specific countries. While the transperineal approach may lower the risk of infection without compromising diagnostic capabilities, it is unknown whether prophylactic antibiotics provide value while adequate training and resources are required for wider implementation. Multiple randomized trials of transrectal versus transperineal are ongoing and will provide necessary comparative effectiveness data.

MRI imaging of the prostate, while commonly utilized, has not been shown to impact meaningful long-term outcomes such as cancer-specific mortality. Even with growing clinical experience with mpMRI and fusion biopsies, there remain some cases concerning GG2+ cancer where the targeted biopsy either did not detect cancer or only detected GG1 disease. While this may be due to false positive mpMRI reading, it is also possible that the lesion was under-sampled (e.g., small target in a difficult to access location). How best to manage these cases (e.g., repeat MRI, repeat targeted biopsy, in-bore biopsy) and evolving MRI protocols, such as biparametric MRI and use of artificial intelligence, requires further study.

Abbreviations

95%CI	95% confidence interval
AHRQ	Agency of Healthcare Research and Quality
AIP	Atypical intraductal proliferation
AMSTAR	Assessment of Multiple Systematic Reviews
AS	Active surveillance
ASAP	Atypical small acinar proliferation
AUA	American Urological Association
AUAER	American Urological Association Education and Research, Inc.
AUC	Area under the curve
BOD	Board of Directors
CDR	Cancer detection rate
DRE	Digital rectal exam
EMR	Electronic medical records
ERSPC	European Randomized Study of Screening for Prostate Cancer
GG	Grade Group
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HGPIN	High-grade prostatic intraepithelial neoplasia
IDC-P	Intraductal carcinoma of prostate
mpMRI	multi-parametric magnetic resonance imaging
MRI	Magnetic resonance imaging
MUSIC	Michigan Urological Surgery Improvement Collaborative
NND	Number needed to diagnose
NNS	Number needed to screen
NPV	Negative predictive value
PBCG	Prostate biopsy collaborative group
PCPT	Prostate cancer prevention trial
PGC	Practice Guidelines Committee
PHI	Prostate health index
PICOTS	populations, interventions, comparators, outcomes, timing, and settings
PI-RADS	Prostate Imaging Reporting & Data System
PLCO	The Prostate, Lung, Colorectal and Ovarian
PRS	Polygenic risk score
PSA	Prostate-specific antigen
QUADAS- 2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomized controlled trial
ROBINS-I	Risk of Bias in Non-Randomized Studies of Intervention
ROC	Receiver operating characteristic curve
SDM	Shared decision-making
SNP	Single nucleotide polymorphism
SQC	Science & Quality Council
SSA	Social security administration
STHLM-3	Stockholm-3
SUO	Society of Urologic Oncology

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DISCLAIMER

This document was written by the Early Detection of Prostate Cancer Panel of the American Urological Association Education and Research, Inc., which was created in 2021. The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the early detection of prostate cancer setting.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (“off label”) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management that are too new to be addressed by this guideline as necessarily experimental or investigational.

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