NCCN Guidelines Version 1.2022
Prostate Cancer Early Detection

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NCCN Guidelines Panel Disclosures
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NCCN Prostate Cancer Early Detection Panel Members

Summary of Guidelines Updates

Introduction (PROSD-1)

Baseline Evaluation, Risk Assessment, and Early Detection Evaluation (PROSD-2)

Further Evaluation and Indications for Biopsy (PROSD-3)

Management of Biopsy Results (PROSD-4)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2022 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 2.2021 include:

**General:** Terminologies modified to be more inclusive of all sexual and gender identities.

**PROSD-2**
- **Baseline evaluation:**
  - First bullet, fourth sub-bullet changed: African ancestry to Black/African American identity
  - Sub-bullet added: Environmental exposure
- **Risk assessment changed:**
  - Age 40–75 y for those with:
    - African ancestry Black/African American individuals

**PROSD-2A**
- **Footnote b revised:** Men of African ancestry Black/African American individuals have a higher incidence of prostate cancer, increased prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to Caucasian individuals men. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Lack of access to care and other social determinants of health are also associated with poor outcomes in this population. Although there are data suggesting a role for heritable genes linked to Black/African American individuals as African ancestry, it is not known with certainty whether genetics rather than access to health care and other social determinants of health are the main drivers of increased risk in this patient population. Many support the recommendation for Black/African American individuals men of African ancestry to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. There is no current evidence to support that screening at an earlier age will result in decreased morbidity and mortality compared to testing at age 45, and earlier screening may increase over-diagnosis. Tsodikov A, et al. Cancer 2017;123:2312-2319.
- **Footnote d added:** Patients with exposure to Agent Orange (eg, many Vietnam War veterans) should be informed that Agent Orange exposure may be associated with an increased risk of high-grade prostate cancer.

**PROSD-3**
- The algorithm has been divided into two branches under Management for high and low suspicion for clinically significant cancer.
  - Bullet added: High suspicion for clinically significant cancer, with management as, ‘Transrectal ultrasound (TRUS)- or transperineal-guided biopsy with or without MRI targeting’
  - Bullet added: Low suspicion for clinically significant cancer, with management as, ‘Follow-up in 6–12 mo with PSA/DRE’
- **Footnote l revised:** Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk. Percent-free PSA may improve cancer detection. The probability of high-grade cancer (Gleason score ≥ 3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, and ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. Extent of validation of these tests across diverse populations is variable. It is not yet known how such tests could be applied in optimal combination with MRI as yet.
- **Footnote m added:** Transperineal biopsy is associated with a lower risk of sepsis and a reduced need for antibiotics compared to TRUS biopsy.
- **Footnote n revised:** Patients with a persistent and significant increase in PSA should be encouraged to undergo biopsy, including patients with a higher PSA density, even if they have a normal MRI.

**PROSD-4**
- **Footnote s modified:** Tests that improve specificity in the post-biopsy setting—including percent-free PSA, 4Kscore, PHI, PCA3, and ConfirmMDx, MPS, and IsoPSA—should be considered in patients thought to be higher risk despite a negative prostate biopsy.
INTRODUCTION

The panel recognizes that prostate cancer represents a true spectrum of disease and that not all patients diagnosed with prostate cancer require treatment. The panel believes that maximizing the detection of early prostate cancer will increase the detection of both indolent (slower-growing) and aggressive (faster-growing) prostate cancers. The challenge is to minimize immediate treatment (overtreatment) of indolent cancers by accurately characterizing the biology of the detected cancer. This guideline highlights several techniques designed to improve the identification of significant cancer while avoiding the detection of indolent disease. Identification and selective treatment of aggressive cancers should result in significant decreases in morbidity and mortality while limiting adverse effects on quality of life. The NCCN Guidelines for Prostate Cancer Early Detection do not address the treatment of prostate cancer. See the NCCN Guidelines for Prostate Cancer for prostate cancer treatment recommendations. It is the intention of the panel that these guidelines be linked. Specifically, early detection strategies that do not recognize the importance of refined and selective treatment may result in harm.

The guidelines are specifically for individuals with a prostate opting to participate in an early detection program (after receiving the appropriate counseling on the pros and cons). It is the majority opinion of the Prostate Cancer Early Detection Panel members that there is a growing population of patients currently being diagnosed with prostate cancer who can, and should, be monitored for their disease rather than immediately treated as presented in the NCCN Guidelines for Prostate Cancer. The guidelines for when to start and stop screening, at what intervals to conduct screening, and when to biopsy were recommended by most panel members, but a consensus was not reached. The guidelines are continuously in a state of evolution, and the panel will incorporate changes based on new evidence and expert opinion and provide a rating of consensus for each recommendation.
BASELINE EVALUATION

- History and physical (H&P) including:
  - Family cancer history
  - Family or personal history of high-risk germline mutations
  - History of prostate disease and cancer early detection, including prior prostate-specific antigen (PSA) and/or isoforms, exams, and biopsies
  - Black/African American identity
  - Medications
  - Environmental exposure

RISK ASSESSMENT

- Start risk and benefit discussion about offering prostate cancer early detection:
  - Baseline PSA
  - Strongly consider baseline digital rectal examination (DRE)

EARLY DETECTION EVALUATION

- Age 45–75 y for average-risk patients
  - PSA <1 ng/mL, DRE normal (if done) → Repeat testing at 2- to 4-year intervals

- Age 40–75 y for:
  - Black/African American individuals
  - Those with germline mutations that increase the risk for prostate cancer
  - Those with suspicious family history
  - PSA 1–3 ng/mL, DRE normal (if done) → Repeat testing at 1- to 2-year intervals
  - PSA >3 ng/mL and/or very suspicious DRE → See Further Evaluation and Indications for Biopsy (PROSD-3)

- Age >75 y, in select patients (category 2B)
  - PSA ≥4 ng/mL or very suspicious DRE → See Further Evaluation and Indications for Biopsy (PROSD-3)

- Not screened → Repeat testing in select patients at 1- to 4-year intervals

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Family or personal cancer history and/or family or personal history of high-risk germline mutations can inform when to begin shared decision-making regarding prostate cancer early detection. Family cancer history includes, but is not limited to, a first- or second-degree relative with metastatic prostate cancer, ovarian cancer, male breast cancer, female breast cancer ≤45 years, colorectal or endometrial cancer ≤50 years, or pancreatic cancer or two or more first- or second-degree relatives with breast, prostate (but not clinically localized Grade Group 1), colorectal, or endometrial cancer at any age. If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. Mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in individuals with germline BRCA2 or HOXB13 mutations occurs earlier and is more likely to be associated with prostate cancer mortality. For individuals with BRCA1, ATM, or mismatch repair (MLH1, MSH2, MSH6, PMS2) germline gene mutations timing of testing is less clear. Consequently, prostate cancer screening is recommended at age 40 years for BRCA2 carriers, and it is reasonable for individuals with other germline mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (CRIT-1) and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (LS-1). Page EC, Eur Urol 2019;76:831-842; Giri VN, et al. J Clin Oncol 2020;38:2798-2811.

Black/African American individuals have a higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to Caucasian individuals. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Lack of access to care and other social determinants of health are also associated with poor outcomes in this population. There are data suggesting a role for heritable genes linked to Black/African American individuals as drivers of increased risk in this patient population. Many support the recommendation for Black/African American individuals to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. There is no current evidence to support that screening at an earlier age will result in decreased morbidity and mortality compared to testing at age 45, and earlier screening may increase over-diagnosis. Tsodikov A, et al. Cancer 2017;123:2312-2319.

Medications such as 5α-reductase inhibitors (finasteride and dutasteride) are known to decrease PSA by approximately 50%. PSA values in these patients should be corrected accordingly.

Patients with exposure to Agent Orange (eg, many Vietnam War veterans) should be informed that Agent Orange exposure may be associated with an increased risk of high-grade prostate cancer.

The best evidence supports the use of serum PSA for the early detection of prostate cancer. DRE should not be used as a stand-alone test. DRE can be considered as a baseline test in addition to serum PSA in all patients, but has its greatest usefulness in those with elevated PSA. Consider referral for biopsy or further testing if DRE is suspicious for cancer at any PSA. Halpern JA, et al. J Urol 2018;199:947-953.

Testing after 75 years of age should be done only in very healthy people with little or no comorbidity (especially if they have never undergone PSA testing or have a rising PSA) to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread testing in this population would substantially increase rates of overdiagnosis and is not recommended.

The median PSA values for those aged 40–49 years range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Individuals who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.

Individuals ≥60 years with a PSA <1.0 ng/mL and those >75 years of age with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases in their lifetime. This low risk is especially true for those in the latter category.
FURTHER EVALUATION AND INDICATIONS FOR BIOPSY

- Repeat PSA
- DRE, if not performed during initial risk assessment
- Workup for benign disease

• Multiparametric MRI, if available\(^i\,k\)
  • Consider biomarkers that improve the specificity of screening\(^j\)

• High suspicion for clinically significant cancer

  Transrectal ultrasound (TRUS)- or transperineal-guided biopsy\(^m\) with or without MRI targeting\(^j\)

• Low suspicion for clinically significant cancer

  Follow-up in 6–12 mo with PSA/DRE\(^n\)

MANAGEMENT

\(^i\) The level of PSA correlates with the risk of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) demonstrated that 15% of individuals with a PSA level ≤4.0 ng/mL and a normal DRE had prostate cancer diagnosed on end-of-study biopsies. Approximately 30% to 35% of those with serum PSA between 4 to 10 ng/mL will be found to have cancer. Total PSA levels >10 ng/mL confer a >67% likelihood of prostate cancer.


\(^k\) A negative MRI does not exclude the possibility of cancer. Consider biomarkers and/or PSA density when deciding whether to avoid a biopsy in a man with a negative mpMRI result.

\(^m\) Transperineal biopsy is associated with a lower risk of sepsis and a reduced need for antibiotics compared to TRUS biopsy.

\(^n\) Patients with a persistent and significant increase in PSA should be encouraged to undergo biopsy, including patients with a higher PSA density, even if they have a normal MRI.

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**MANAGEMENT OF BIOSPY RESULTS**

**Cancer**

- **Intraductal carcinoma (IDC) without invasive carcinoma**
  - See NCCN Guidelines for Prostate Cancer
  - or
  - Repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma

- **Atypical intraductal proliferation (AIP) without invasive carcinoma**
  - Repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma

- **Atypia, suspicious for cancer**
  - Follow-up:
    - Consider biomarkers that improve the specificity of screening and/or multiparametric MRI
    - Consider repeated biopsy with relative increased sampling of the atypical site

- **High-grade prostatic intraepithelial neoplasia (PIN)**
  - Follow-up:
    - PSA and DRE at 6- to 24-month intervals
    - Consider biomarkers that improve the specificity of screening and/or multiparametric MRI
  - Repeat prostate biopsy with refined biopsy techniques, based on risk

- **Benign**
  - See NCCN Guidelines for Prostate Cancer
  - or
  - Repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma

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**PROSD-4**

- IDC represents an independent adverse pathologic factor in both radical prostatectomy and needle biopsy specimens. Its presence in biopsy material strongly suggests the presence of high-grade cancer. Consideration should be given to initial treatment; otherwise, careful evaluation is indicated, with strong consideration given to repeat biopsy using MRI guidance. Porter LH, et al. Eur Urol 2017;72:492-495.

- Intraductal proliferations may show a greater degree of architectural complexity and/or cytologic atypia than typical high-grade PIN, yet falling short of the strict diagnostic threshold for IDC. The preferred terminology for these lesions is AIP. When diagnosed on needle biopsy, AIP is potentially considered a marker of unsampled cancer, and it is associated with an increased risk (50%) of invasive carcinoma and/or IDC-P on repeat biopsy. Shah RB, et al. Histopathology 2019;75:346-353.

- It is well known that a negative prostate biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. Those patients with negative prostate biopsies should be followed with DRE and PSA with consideration of multiparametric MRI and biomarker tests that improve the specificity of PSA testing.

- PSA testing may be discontinued at certain ages and PSA cutpoints. See Discussion.

- Tests that improve specificity in the post-biopsy setting—including percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, MPS, and IsoPSA—should be considered in patients thought to be higher risk despite a negative prostate biopsy (See PROSD-3).

- Multiparametric MRI and/or use of refined prostate biopsy techniques (image guidance using MRI/ultrasound fusion) may help identify regions of cancer missed on prior prostate biopsies and are recommended after at least 1 negative prostate biopsy and high suspicion for cancer based on PSA and/or biomarkers. Multiparametric MRI followed by lesion targeting increases the detection of clinically significant, higher-risk disease while lowering the detection of lower-risk disease. Although some advocate for excluding systematic biopsy in those undergo MRI targeting, most advocate for a combined approach as some high-grade cancers are uniquely detected using the systematic approach.
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Prostate Cancer Early Detection

NCCN Categories of Evidence and Consensus

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<td>Category 1</td>
<td>Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</td>
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<td>Category 2A</td>
<td>Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</td>
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<tr>
<td>Category 2B</td>
<td>Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.</td>
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<tr>
<td>Category 3</td>
<td>Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.</td>
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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Introduction
Prostate cancer represents a spectrum of disease that ranges from non-aggressive, slow-growing disease that may not require treatment to aggressive, fast-growing disease that does. The NCCN Guidelines for Prostate Cancer Early Detection provide a set of sequential recommendations detailing an early detection and evaluation strategy for maximizing the detection of prostate cancer that is effectively treatable and that, if left undetected, represents a risk to the patient.

These guidelines focus on minimizing unnecessary procedures and limiting the detection of indolent disease. These guidelines were developed for individuals who have elected to participate in the early detection of prostate cancer. The panel does not support unselected and uninformed population-based screening. The panel supports an early detection program only in healthy patients. Any clinician who uses these guidelines is expected to exercise independent medical judgment in the context of individual clinical circumstances, and to fully incorporate patient preferences in deciding how to apply these guidelines.

Overview
Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths in American males. In 2021, it is estimated that 248,530 Americans will be diagnosed with prostate cancer and 34,130 will die of this disease.\(^1\) During the same period, nearly 20 million individuals in the United States will be confronted with important decisions regarding early detection for prostate cancer. Those with a prostate in the United States have about 1 chance in 9 of eventually being diagnosed with this malignancy and about 1 chance in 41 of eventually dying of it.\(^2\) From 1993 to 2018, death rates from prostate cancer in the United States fell by 52%, largely due to early detection and improved treatment, although death rates stabilized in the last few years of that period.\(^1,3\)

The panel supports the continued use of prostate-specific antigen (PSA) testing for the early detection of prostate cancer in informed, healthy individuals in certain age groups. The panel bases this recommendation on level I evidence from randomized trials that observed a reduction in prostate cancer-specific mortality in those who underwent PSA screening. However, the panel also uniformly acknowledges the risk of overdetection of otherwise indolent disease and the attendant risk of overtreatment, which exposes patients to the potential morbidity of treatment without benefit. Therefore, these guidelines highlight several techniques designed to improve the identification of significant cancer while avoiding the detection of indolent disease. The panel also concludes that these NCCN Guidelines for Prostate Cancer Early Detection should be used in conjunction with the NCCN Guidelines for Prostate Cancer (available at www.NCCN.org), which explicitly recommend active surveillance or observation for appropriate candidates.

Literature Search Criteria and Guidelines Update

Methodology

Prior to the update of this version of the NCCN Guidelines for Prostate Cancer Early Detection, an electronic search of the PubMed database was performed to obtain key literature in the field of prostate cancer early detection using the following search terms: (prostate cancer) AND (screening OR early detection). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.\(^4\)

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Validation Studies; and Systematic Reviews.
The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Types of Early Detection Testing

PSA Testing

PSA is a glycoprotein secreted by prostatic epithelial cells, and its protease activity lysed the clotted ejaculate to enhance sperm motility. Although primarily confined to the seminal plasma, PSA enters the circulation through unknown mechanisms. Many commercially available sources of PSA antibodies for serum tests are available worldwide. With the exception of minor differences in the calibration of these assays, they perform comparably when used appropriately. However, PSA measures obtained using different commercial assays are not directly comparable or interchangeable, since the values are calibrated against different standards. If an abnormally high PSA is observed, repeat testing should be performed, particularly if the value is close to the threshold value that prompts evaluation. One study showed that approximately 25% of individuals with initial PSA levels between 4 and 10 ng/mL had normal PSA values upon repeat testing.5

PSA is not a cancer-specific marker, and as such most individuals with elevated PSA levels do not have prostate cancer. The risk of prostate cancer increases with increasing PSA, but there is no level of PSA below which the risk of prostate cancer can be eliminated. Total PSA (tPSA) levels greater than 10 ng/mL confer a greater than 67% likelihood of biopsy-detectable prostate cancer, and only about 18% of patients with PSA in the 4 to 10 ng/mL range have a subsequent positive biopsy.6,7 Still, individuals with low PSA values have a significant chance of having prostate cancer. Using data from 18,882 participants in the Prostate Cancer Prevention Trial (PCPT), Thompson et al demonstrated that 15% of those with a PSA level of 4.0 ng/mL or less and a normal DRE had prostate cancer (as diagnosed by end-of-study biopsies).8 The PCPT investigators determined the sensitivity and specificity of PSA levels for detecting any prostate cancer using various cut-offs. At 3.1 ng/mL, PSA has a sensitivity of about 32% and a specificity of about 87%.9

Overall, appropriate use of PSA testing alone can provide a diagnostic lead-time of 5 to 10 years, but the lead-time varies across studies, populations, and screening protocols.10 Since the introduction of PSA testing, there has been an increase in the detection of early-stage, organ-confined disease and a decrease in disease that is metastatic at the time of diagnosis.11

Despite its limitations, recent population-based prostate cancer screening studies have demonstrated survival benefits using PSA—sometimes in combination with digital rectal examination (DRE) or other ancillary tests, as discussed in more detail below.

Factors Affecting PSA Levels

PSA can be elevated due to infection, recent instrumentation, ejaculation, or trauma. However, empiric antibiotic use appears to have little value for improving test performance in asymptomatic patients with an elevated PSA.12

The 5α-reductase inhibitors (5-ARIs) finasteride and dutasteride are commonly used to treat lower urinary tract symptoms due to benign prostatic hyperplasia (BPH). Use and duration of 5-ARI therapy should be elicited carefully in the history, because this class of drugs typically results...
in an approximate 50% decrease in serum PSA levels within 6 to 12 months of initiating therapy.\textsuperscript{13} However, this effect is tremendously variable. For example, one study showed that after 12 months of treatment, only 35% of patients demonstrated the expected 40% to 60% decrease in PSA, while another 30% had greater than a 60% decrease.\textsuperscript{14} Thus, the commonly employed method of doubling the measured PSA value to obtain an adjusted value may result in unreliable cancer detection.

In fact, failure to achieve a significant PSA decrease while taking 5-ARIs can indicate a heightened risk for prostate cancer that warrants regular testing. Results from several clinical trials suggested that 5-ARIs enhance the predictive capacity of PSA.\textsuperscript{15-17} Although reflex ranges for PSA among patients on 5-ARIs have not been established, a confirmed rise from post-5-ARI treatment nadir may be a better indication for biopsy than doubling the PSA level.

The PCPT of 18,882 participants demonstrated that finasteride reduced the incidence of prostate cancer by 25% compared to placebo.\textsuperscript{18} The decreased risk persisted at 21% through 16 years of follow-up.\textsuperscript{19} This reduction was almost exclusively for low-grade (Grade Group 1) tumors; an increased proportion of aggressive (Grade Group ≥2) tumors was seen. However, after 18 years of follow-up, there was no significant difference in overall survival or survival after the diagnosis of prostate cancer in those on finasteride compared to the control group.\textsuperscript{20} In addition, after a median follow-up of 18.4 years, fewer deaths due to prostate cancer were seen in the finasteride group.\textsuperscript{21} Although this difference was not statistically significant, the results suggest that earlier fears that increased high-grade prostate cancer detection would cause an increase in prostate cancer mortality were unfounded.

In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, PSA detected more high-grade tumors in the dutasteride arm, while the overall prostate cancer diagnosis fell by 23% compared to control.\textsuperscript{15} Similar to the PCPT trial, the difference in the number of high-grade cancers detected did not result in a mortality difference.\textsuperscript{22}

A report on the CombAT trial also showed a 40% lower incidence of prostate cancer with dutasteride plus tamsulosin (another BPH drug) compared to tamsulosin alone, along with a slightly improved yield of PSA-driven biopsy.\textsuperscript{17} Unlike the PCPT and REDUCE studies, diagnosis of high-grade (Grade Group ≥2) tumors was not increased.

A population-based prospective study using data from 333,820 participants in the Stockholm PSA and Biopsy Register and Prescribed Drug Register found that 5-ARI exposure decreased the risk for prostate cancer overall and for prostate cancer of Grade Group ≤3, with longer courses resulting in a larger decreased risk.\textsuperscript{23} Grade Group 4–5 prostate cancer risk was unaffected by 5-ARI treatment.

Overall, these studies suggest that PSA testing may have enhanced specificity for patients receiving finasteride or dutasteride. However, in a population-based cohort study, researchers analyzed more than 80,000 records of patients with prostate cancer and found that use of 5-ARI before diagnosis was associated with delayed diagnosis, higher stage at diagnosis, higher prostate cancer–specific mortality, and higher all-cause mortality.\textsuperscript{24} Whether or not individuals should consider taking these agents for chemoprevention is beyond the scope of this guideline.

It should also be noted that finasteride at 1 mg/day used to treat male pattern baldness also lowers serum PSA.\textsuperscript{13}

Ketoconazole, commonly used to treat fungal conditions, inhibits the androgen synthesis pathway and hence can also lower PSA levels. Since moderate PSA decreases have been observed with ketoconazole in the
treatment of patients with prostate cancer after failure of hormonal therapy, recent ketoconazole use should also be noted in the history.

A health survey on 12,457 people visiting a prostate cancer screening clinic showed that greater than 20% took herbal supplements, while only 10% took a prescription medication (such as finasteride) to help treat lower urinary tract symptoms. Several of these herbal supplements, such as saw palmetto, may contain phytoestrogenic compounds that can affect serum PSA levels. Very little is known about the exact composition of these herbal supplements and their specific effects on serum PSA levels.

Controversies of PSA Testing
The decision about whether to pursue early detection of prostate cancer is complex. When, who, and how often to test remain major topics of debate. PSA screening has played a critical role in the downward migration of prostate cancer stage seen over the past decades. The incidence of metastatic disease at the time of diagnosis has decreased dramatically since 1988. This trend has likely, but not positively, contributed to a substantial reduction in prostate cancer mortality.

Still, although prostate cancer is a major cause of death and disability in the United States, many argue that the benefits of early detection are, at best, moderate, and that early detection often results in overtreatment, which is the identification of disease that would not be a problem for the patient if undetected or untreated and that would not have been identified without screening. These arguments hold that overtreatment may lead to overtriage, which is aggressive treatment in individuals with a low probability of yielding clinical benefit. However, analyses of recent trends in prostate cancer management show that the rates of active surveillance for early-stage disease have increased significantly, allaying initial concerns about overtreatment. In addition, PSA testing often produces false-positive results, which in turn contribute to patient anxiety and the increased costs and potential complications associated with unnecessary biopsies.

On the basis of its perception of the harm-benefit tradeoffs of prostate cancer screening, the U.S. Preventive Services Task Force (USPSTF) recommended against routine PSA testing in 2012. After this recommendation, prostate cancer screening decreased, as did biopsy rates, diagnoses of localized prostate cancers, and radical prostatectomy rates. The effect of the 2012 USPSTF recommendations on the rate of metastatic prostate cancer diagnoses is, however, unclear, with some studies showing an increase and others showing none.

The USPSTF released updated recommendations in 2018 based on an evidence report and systematic review. The recommendations are: 1) against PSA-based prostate cancer screening in individuals aged 70 years and older; and 2) for individualized, informed decision-making regarding prostate cancer screening in individuals aged 55 to 69 years. For those in this younger age group, clinicians should inform them regarding the potential harms and benefits of PSA-based screening. The USPSTF statement does not provide guidance for people younger than 55 years.

DRE
Best evidence supports the use of serum PSA for the early detection of prostate cancer. Still, many experts continue to recommend DRE for screening, as some clinically significant cancers may potentially be missed using a serum PSA cut-point alone. Studies have consistently shown that prostate cancer cases detected through PSA testing are more often confined to the prostate than those detected solely by DRE. Currently, 81% of prostate cancers are pathologically organ-confined at time of diagnosis.

Recent screening trials have used DRE either in conjunction with PSA for screening or as an ancillary test for patients who are found to have an
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Elevated PSA. To elucidate the specific role of DRE in screening for prostate cancer, Gosselaar and colleagues showed that among those with a serum PSA greater than 3 ng/mL, those with a positive DRE were more likely to have prostate cancer. Furthermore, among 5519 participants in the control arm of the PCPT, Thompson and colleagues observed that an abnormal DRE increased the probability of cancer detection by almost 2.5-fold in multivariable analysis; the risk of high-grade disease was increased 2.7-fold with an abnormal DRE. An analysis of the PLCO trial found that a suspicious DRE was associated with the identification of Grade Group ≥2 prostate cancer in those with a PSA ≥3 ng/mL (23.0% risk at 10 years vs. 13.7% risk at 10 years in those with a non-suspicious DRE), but not in those with a PSA <2 ng/mL (1.5% vs. 0.7%). Ten-year risk in those with a PSA in the 2 to 3 ng/mL range were 6.5% in individuals with a suspicious DRE compared with 3.5% in individuals with a non-suspicious DRE.

In a secondary analysis of the PLCO trial, in which participants were screened with a PSA and DRE, only 15.4% of participants with a suspicious DRE had an elevated PSA. On multivariate analysis, a suspicious DRE was associated with an increased risk of clinically significant prostate cancer (HR, 2.21; 95% CI, 1.99–2.44; P < .001) and prostate cancer-specific mortality (HR, 2.54; 95% CI, 1.41–4.58; P = .002). However, PSA was associated with an even greater risk in both cases: clinically significant prostate cancer (HR, 5.48; 95% CI, 5.05–5.96; P < .001) and prostate-cancer-specific mortality (HR, 5.23; 95% CI, 3.08–8.88; P < .001).

A prospective clinical trial in 6630 individuals directly compared the efficacy of PSA and DRE in the early detection of prostate cancer. The cancer detection rates were 3.2% for DRE, 4.6% for PSA, and 5.8% for DRE plus PSA. The positive predictive values (PPVs) were 32% for PSA and 21% for DRE.

Overall, the PPV of a DRE in individuals with a normal PSA is poor (about 4%–21%). Therefore, an abnormal DRE result alone as an indication for biopsy would lead to a large number of unnecessary biopsies and the detection of many insignificant cancers in individuals with low PSA values. In fact, in an analysis of 166,104 individuals with prostate cancer diagnosed between 2004 and 2007 from the SEER database, only 685 (0.4%) had palpable, PSA-occult (PSA level of <2.5 ng/mL), Grade Group ≥4 prostate cancer.

Overall, the panel believes that the value of a DRE as a stand-alone test for prostate detection is limited, even though a DRE picks up some cases of advanced cancer that would otherwise be missed. Therefore, the panel believes that DRE should not be used as a stand-alone test without PSA testing. Instead, the panel recommends DRE as a complementary test that can be considered with serum PSA in asymptomatic individuals who had a risk/benefit discussion and decided to pursue screening for prostate cancer. The panel notes that the greatest usefulness of DRE is in those with elevated PSA (see Pre-Biopsy Workup, below). Those with a DRE that is very suspicious for cancer should be considered for biopsy or further testing regardless of PSA results. Furthermore, the panel believes that DRE should be performed in all individuals with an abnormal serum PSA to aid in decisions regarding biopsy (see Pre-Biopsy Workup, below).

Population-Based Screening Studies

Although many trials have been cited with regard to PSA testing, two studies are most relevant due to their topicality and randomized design.

ERSPC Trial

The ERSPC trial involved about 182,000 participants between the ages of 50 and 74 years in seven European countries, randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening; DRE or...
other ancillary tests were also performed in the screening group. The predefined core group included 162,388 participants aged 55 to 69 years. Death from prostate cancer was the primary outcome. During a median follow-up of 11 years, the cumulative incidence of prostate cancer was 7.4% in the screening group versus 5.1% in the control group. There were 299 prostate cancer deaths in the screening group compared to 462 in the control group. The rate ratio for death from prostate cancer was 0.79 for the screening arm compared to the control arm (95% CI, 0.68–0.91; \( P = .001 \)). The investigators concluded that the PSA-based screening program reduced mortality from prostate cancer by 21%. At the time of publication, the authors stated that 1055 individuals would need to be screened and 37 additional individuals would need to be treated over 11 years to prevent one prostate cancer death. Modeling the ERSPC data, however, Heijnsdijk and colleagues estimated that the number needed to screen was 98 and the number needed to treat was 5 to prevent one prostate cancer death.

A report of 13-year follow-up of the ERSPC trial, with 7408 cases of prostate cancer diagnosed in the screening arm and 6107 cases diagnosed in the control arm, confirmed these results. The unadjusted rate ratio for death from prostate cancer was 0.79 (95% CI, 0.69–0.91) at 13 years. After adjusting for non-participation, the rate ratio of prostate cancer death was 0.73 (95% CI, 0.61–0.88). The authors reported that, for 781 individuals invited for screening or 27 additional prostate cancers detected, one prostate cancer death could be averted. Furthermore, another analysis of these 13-year data found that fewer participants were diagnosed with metastatic disease in the screening arm (incidence rate ratio, 0.60; 95% CI, 0.52–0.70). After longer follow-up (16 years), the number invited for screening and the number of prostate cancers detected to avert one prostate cancer death were reduced to 570 and 18, respectively.

The apparent risk reduction was also confirmed in an analysis of the Rotterdam section of the ERSPC trial where prostate cancer-specific mortality was reduced by 32%. This same group found that if one controlled for noncompliance and nonattendance, the risk of death due to prostate cancer could be reduced by up to 51%.

The Finnish Prostate Cancer Screening Trial, the largest component of ERSPC, reported a small, non-statistically significant reduction in prostate cancer-specific death after 12 years of follow-up. The Göteborg randomized, population-based, prostate cancer screening trial was initiated before and independently of the ERSPC, but some of its patients were reported as part of the ERSPC. Twenty thousand individuals aged 50 to 64 years were randomized to either a screening group invited for PSA testing every 2 years or to a control group not invited. The study is ongoing, with participants who have not reached the upper age limit invited for PSA testing. In those randomized to screening, 76% attended at least one test. PSA testing in the general population was very low at the beginning (3%), but increased over time. During a median follow-up of 14 years, 1138 participants in the screening group and 718 in the control group were diagnosed with prostate cancer, resulting in a cumulative prostate cancer incidence of 12.7% in the screening group and 8.2% in the control group (HR, 1.64; 95% CI, 1.50–1.80; \( P < .0001 \)). The rate ratio for death from prostate cancer was 0.56 (95% CI, 0.39–0.82; \( P = .002 \)) in the screening group compared with the control group. Overall, 293 individuals needed to be screened and 12 needed to be diagnosed to prevent one prostate cancer death over 14 years. This study shows that prostate cancer screening is acceptable to the Swedish population and that prostate cancer mortality was reduced almost by half over 14 years. In addition, it should be noted that a cause-specific survival benefit was noted despite the fact that not all cancers were immediately treated. This result suggests that early detection combined with selective treatment...
based on risk can lower mortality rates without uniform treatment of all cancers.

Eighteen-year follow-up of the Göteborg trial was reported, with 1396 cases of prostate cancer in the screening arm and 962 cases in the control arm. The reduction in absolute prostate cancer-specific mortality was 0.72 (95% CI, 0.50–0.94). The number needed to invite to prevent one death was 139 and the number needed to diagnose was 13.

There are several possible explanations for the more favorable results of the Göteborg trial compared to the PLCO (see below) or ERSPC trials. First, the patients were younger and less likely to have incurable prostate cancer at first screening; second, there was less contamination of the control arm because PSA testing was uncommon in the Swedish population when the study began; third, a lower PSA threshold was used for recommending a biopsy; and finally, participants were screened more frequently than in ERSPC and for a longer period than in PLCO. However, because more than half of the participants were included in the main analysis of ERSPC, the Göteborg trial should not be interpreted as a true independent confirmatory study. An analysis of the Göteborg trial showed that the risks of aggressive prostate cancer and prostate cancer mortality became similar in the screening and control arms 9 years after screening cessation.

PLCO Trial
The PLCO study randomized 76,685 individuals aged 55 to 74 years at 10 U.S. study centers to annual screening (annual PSA for 6 years and DRE for 4 years) or usual care. After 13 years of follow-up, the incidence rate ratio for the screening arm compared to the control arm was 1.12 (95% CI, 1.07–1.17). The investigators did not find a statistically significant difference between the disease-specific mortality rates of the screening and control groups (RR, 1.09; 95% CI, 0.87–1.36). Results were similar after 15-year follow-up.

Despite the large sample size, this trial was flawed both by prescreening and the high contamination rate of 40% to 52% per year in the control group (ie, 74% of participants in the usual care arm were screened at least once). The high contamination rates have been confirmed by others. The estimated mean number of screening PSAs (DREs) was 2.7 (1.1) in the control arm and 5.0 (3.5) in the screened arm. In addition, the biopsy rate for those with elevated serum PSA values was relatively low compared to the European trials. The PLCO trial thus really compared fixed screening versus “opportunistic” screening and, therefore, did not really test the hypothesis that screening with PSA is of value. However, it did show that yearly screening may be of limited value compared to less frequent testing.

An analysis, which endeavored to account for the increased screening and diagnostic workup in the control arms of the PLCO and ERSPC, found that PSA screening lowered the risk for prostate cancer death in both trials by similar amounts (by an estimated 25% to 31% in PLCO and by an estimated 27% to 32% in ERSPC).

In a subset analysis of PLCO reported by Crawford and colleagues, a 44% decrease in the risk of prostate cancer-specific death was observed in those with no or minimal comorbidity assigned to screening compared to control, and the numbers needed to screen and treat to prevent one death were 723 and 5, respectively. This benefit was not found among individuals with one or more significant comorbidities. These results suggest that screening is more useful among individuals in good health due to the lack of competing cause for mortality. However, others suggest that such analysis is prone to major methodologic errors.
CAP Trial

The results of the Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP) were recently reported. Men aged 50 to 69 years (N = 419,582) were randomized to a single PSA test or no screening. After a median follow-up of 10 years, 549 participants died of prostate cancer in the intervention group versus 647 in the control group (P = .50). Not surprisingly, more low-risk cancers were identified in the intervention group. No difference in all-cause mortality was seen. Although this trial had several very important strengths, it had limitations as well. Only a single PSA test was used, a standard 10-core biopsy was undertaken, the median follow-up was 10 years, and there was only 40% compliance with the intervention (biopsy). Serial testing, better compliance, longer follow-up, and use of additional technology preceding biopsy (discussed below) may lead to greater benefit with PSA testing.

Trial Limitations

In addition to the limitations of the PLCO trial noted previously, these randomized controlled trials (RCTs) also share at least three additional limitations. First, they did not address the potential benefit of screening in those with high-risk factors. For instance, less than 5% of PLCO participants were of African-American descent and only 7% reported a family history of prostate cancer. Therefore, it is not known whether men at higher risk may benefit more from screening than those at lower risk. Second, many individuals in these studies underwent sextant prostate biopsies rather than extended core biopsies, the standard diagnostic technique used today. The ERSPC may have underestimated benefit due to advanced age at first PSA test (median >60 years), low intensity of screening (largely every 4 years) and, perhaps, suboptimal treatment available in Europe in the 1990s compared to what is available today. The reduction in prostate cancer mortality must be balanced against the adverse effects of treatment, emphasizing the importance of selective rather than universal treatment of individuals with prostate cancer identified by screening.

Practical Considerations of Testing

Age at Which to Initiate Testing

Controversy exists as to the ideal age to begin screening for prostate cancer. Recent randomized trials looking at the impact of screening on prostate cancer mortality have focused primarily on individuals aged 55 to 69 years. The ERSPC and Göteborg trials reported decreased disease-specific mortality in individuals aged 55 to 69 and 50 to 64 years, respectively. These results support baseline PSA testing in individuals aged 50 to 55 years with the strongest evidence supporting testing at age 55 years. Recent analyses of PSA testing in Swedish individuals aged 50 to 54 years support screening in this younger cohort.

As even younger individuals were not included in these screening studies, baseline testing at earlier ages has not been evaluated in RCTs. However, observational evidence suggests that baseline testing of individuals in their 40s and early 50s may have value for future risk stratification, although some would describe the value as marginal. A study by Lilja and colleagues assessed blood collected from 21,277 participants in Sweden aged 33 to 50 years who were followed until 2006. Among the 1312 cases of prostate cancer and 3728 controls without prostate cancer, these investigators reported that a single PSA test before age 50 years predicted subsequent prostate cancer up to 30 years later with a robust area under the curve (AUC) of 0.72 (0.75 for advanced prostate cancer). However, the possible risks of unnecessary biopsies and prostate cancer overdetection should be acknowledged with earlier initiation of screening.

Another report clarified associations of age with the long-term risks of metastases. In this study, the risk of prostate cancer death was strongly...
correlated with baseline PSA in individuals aged 45 to 49 years and 51 to 55 years; 44% of the deaths in the analytic cohort occurred in participants in the highest tenth of the distribution of PSA, suggesting that there may be a strong rationale for baseline testing in those younger than age 55 years.

In a nested case-control study of individuals 40 to 59 years of age in the Physicians' Health Study, baseline PSA strongly predicted lethal prostate cancer later in life. For example, those aged 55 to 59 years with PSA levels above the 90th percentile had an odds ratio (OR) of 6.9 (95% CI, 2.5–19.1) for lethal prostate cancer compared with those whose PSA levels were at or below the median. A secondary analysis of a cohort in the PLCO trial also found a strong correlation between baseline PSA levels in participants aged 55 to 60 years and the actuarial 13-year incidence of clinically significant prostate cancer. Those with baseline PSA levels of ≤0.49 ng/mL, 0.50–0.99 ng/mL, 1.00–1.99 ng/mL, 2.00–2.99 ng/mL, 3.00–3.99 ng/mL, and ≥4.00 ng/mL had incidence rates of 0.4% (95% CI, 0.0–0.8%), 1.5% (95% CI, 1.1–1.9%), 5.4% (95% CI, 4.4–6.4%), 10.6% (95% CI, 8.3–12.9%), 15.3% (95% CI, 11.4–19.2%), and 29.5% (95% CI, 24.2–34.8%), respectively (all pairwise log-rank P ≤ .004).

Taken together, these results suggest that one could perform early baseline testing and then determine the frequency of testing based on risk. Although many physicians advocate earlier testing only in individuals thought to be at higher risk due to family history or African ancestry, a baseline serum PSA is a stronger predictor of the future risk of the disease compared to either of these risk factors.

Most panel members favor informed testing beginning at age 45 years. Repeat testing at 1- to 2-year intervals is recommended for individuals who have a PSA value ≥1.0 ng/mL and at 2- to 4-year intervals for individuals with a PSA <1 ng/mL (also see Frequency of Testing, below).

This value is above the 75th percentile for younger individuals (<50 years). The median PSA levels are 0.7 ng/mL and 0.9 ng/mL for ages 40 to 49 years and 50 to 59 years, respectively.

**Frequency of Testing**

Current guidelines and recent screening trials have employed varying strategies with regard to the frequency of prostate cancer screening. The ideal screening interval to maximize mortality reduction yet minimize overdiagnosis remains uncertain.

A recent comparison of two centers involved in the ERSPC trial studied the impact of different screening intervals on the diagnosis of interval cancers in participants aged 55 to 64 years. The Göteborg arm randomized 4202 participants to screening every 2 years, while the Rotterdam arm randomized 13,301 participants to screening every 4 years with similar follow-up of 11 to 12 years. Compared to screening every 4 years, there was a significant 43% reduction in the diagnosis of advanced prostate cancer (clinical stage >T3a, N1, or M1; PSA >20 ng/mL; Grade Group 5 at biopsy) for screening every 2 years. However, there was also a 46% increase in the diagnosis of low-risk prostate cancer (clinical stage T1c, Gleason <6, and PSA <10 ng/mL at biopsy) for screening every 2 years.

Another study using microsimulation models of prostate cancer incidence and mortality predicted that a strategy that utilizes biennial intervals for those with average PSA levels and longer screening intervals (every 5 years) for those with low PSA levels (below median for age by decade) allows a 2.27% risk of prostate cancer death compared to 2.86% from no screening. In addition, compared to annual screening and using a biopsy threshold of 4.0 ng/mL, the biennial strategy also projected a relatively lower overdiagnosis rate of 2.4% (vs. 3.3% for annual screening), a 59% reduction in total tests, and a 50% reduction in false-positive results. The
biennial model was robust to sensitivity analyses, which varied the range of cancer incidence and survival attributed to screening.

Few studies have addressed the effect of PSA levels on the interval of testing, but it appears that individuals with a very low PSA could safely extend the testing interval. In the Rotterdam section of the ERSPC trial, participants with a PSA less than 1 ng/mL had a very low risk for cancer at 4 and 8 years (0.23% and 0.49%). Other studies have shown that PSA values at younger ages strongly predict the development of or death from prostate cancer. For example, in a Swedish case-control study of 1167 individuals, those aged 60 years with PSA concentrations of ≤1 ng/mL had only a 0.5% risk of metastasis by age 85 and a 0.2% risk of death from prostate cancer. Microsimulation models suggest that PSA-based screening intervals (with less frequent screening in those with low PSAs) could substantially reduce the testing burden while preserving the lives saved.

After considering these data, the panel concluded that tailoring screening intervals based on PSA levels might maximize survival advantage while decreasing the number of screenings and limiting overdiagnosis. The panel recommends repeat testing every 2 to 4 years if PSA is <1 ng/mL and every 1 to 2 years if PSA is 1 to 3 ng/mL in individuals aged 45 to 75 years. The panel notes that a younger individual on the higher end of PSA (eg, a 45-year-old with PSA 0.9 ng/mL) might be screened in 2 years, whereas an older individual with a lower PSA might be screened in 4 years. Clinical judgment should be used.

Age at Which to Discontinue Testing

Even more elusive than identifying the ideal age at which to start screening is determining the ideal age at which to discontinue screening for individuals with normal PSA levels.

Panelists uniformly agreed that PSA testing should only be offered to individuals with a 10 or more year life expectancy. However, panelists did not agree as to when to discontinue routine testing in asymptomatic older individuals. Furthermore, estimates of life expectancy can be refined using several resources such as life insurance tables. Physicians may not be accurate at estimating life expectancy and many tend to overvalue age and undervalue comorbidity. Since the previously cited RCTs (ERSPC, PLCO, and Göteborg) observed benefits to testing only in participants aged up to 70 years, several panelists favored stopping testing at age 70 years.

However, other data would suggest a benefit to screening beyond 70 years. A study of 4561 patients who underwent radical prostatectomy found that those older than 70 years were more likely to have higher grade and stage of disease and worse survival compared to their younger counterparts. Others have published similar findings. To assess the appropriate ages for discontinuing screening, the previously cited microsimulation model predicted that decreasing the stopping age from 74 to 69 years would lead to a 27% relative reduction in the probability of life saved, but to an almost 50% reduction in the probability of overdiagnosis. This latter finding reflects the fact that a large proportion of individuals older than 70 years have cancer that would be unlikely to diminish their life expectancy, and that screening in this population would substantially increase rates of overdiagnosis, while also recognizing the increased prevalence of higher-risk cases in this age that could benefit from earlier detection.

The microsimulation model also assessed a strategy of screening individuals up to age 74 years while simultaneously increasing the PSA threshold for biopsy based on age-dependent PSA levels (ie, increasing the threshold level for biopsy with increasing age). Compared to using a
uniform cutoff of 4.0 ng/mL, this strategy reduced the rate of overdiagnosis by one third while only slightly altering lives saved.

$tPSA$ at certain ages may predict future risk. Vickers and colleagues\textsuperscript{101} examined the relationship between baseline PSA at age 60 years and the future risk of prostate cancer death or metastases and found that those with a PSA level below the median (<1 ng/mL) were unlikely to develop clinically significant prostate cancer (0.5% risk of metastases and 0.2% risk of prostate cancer death). Similarly, in a study of 849 individuals in the Baltimore Longitudinal Study of Aging (BLSA), no individuals aged 75 to 80 years with a PSA less than 3.0 ng/mL died of prostate cancer.\textsuperscript{110} Moreover, the time to death or diagnosis of aggressive prostate cancer was longer in those with a PSA <3.0 ng/mL versus those with a PSA >3.0 ng/mL, suggesting that individuals 75 years or older with a PSA <3.0 ng/mL are unlikely to die or experience aggressive prostate cancer throughout their remaining life and most may safely discontinue screening.

In summary, many possible strategies to reduce overdiagnosis in the older population exist. Individuals ≥60 years with a PSA <1.0 ng/mL and those >75 years with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases. Continuing screening beyond age 75 years should be performed only with caution in very healthy patients with little to no comorbidity, especially if they have never undergone PSA testing or have increasing PSA levels (category 2B for continuing screening beyond age 75 years), to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop.

Widespread testing in this population would substantially increase rates of overdiagnosis and is not recommended. Older individuals who do choose to continue PSA-based prostate cancer early detection (category 2B) and who have a PSA <4 ng/mL, a normal DRE (if done), and no other indications for biopsy can undergo repeat testing at 1- to 4-year intervals, but again only in very select patients. Those with a PSA ≥4 ng/mL and/or a DRE that is very suspicious for cancer should be considered for biopsy as indicated in the guidelines.

**Screening in High-Risk Populations**

African-Americans and those with a first-degree relative with prostate cancer (especially cancer found at a younger age) have a higher risk of developing prostate cancer.\textsuperscript{111-117}

**Family History**

Having a first-degree relative with prostate cancer diagnosed before the age of 60 increases the likelihood of a prostate cancer diagnosis by 2.1- to 2.5-fold.\textsuperscript{113,114} Furthermore, in individuals who have a brother with aggressive prostate cancer, the OR for aggressive prostate cancer is 1.21 (95% CI, 1.04–1.39).\textsuperscript{118} A population-based study in Sweden found that the risk for the development of prostate cancer increased with the number of affected relatives.\textsuperscript{119} Data, however, suggest that prostate cancer in individuals with a family history of prostate cancer is not more likely to be aggressive, and cancer-specific outcomes are similar between those with and without a family history.\textsuperscript{116,120,121}

Prostate cancer risk is also elevated in patients with a family history of breast cancer (also see Genetic Syndromes, below).\textsuperscript{122,123}

It is also important to note that, because those with a family history of prostate cancer are more likely to undergo screening and biopsy than those without a family history, the role of family history as a risk factor for prostate cancer may be overestimated.\textsuperscript{124} Welch and Brawley refer to this phenomenon as “self-fulfilling risk factors” in cancers that are “scrutiny-dependent.”\textsuperscript{125}
Genetic Syndromes

Recent data indicate that patients with prostate cancer may have germline mutations in 1 of 16 DNA repair genes: *BRCA2* (5%), *ATM* (2%), *CHEK2* (2%), *BRCA1* (1%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*. Individuals with these inherited syndromes may have an increased risk for prostate cancer. For example, individuals with Lynch syndrome (germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) have a 2- to 5.8-fold increase in risk for prostate cancer. Age of onset and aggressiveness of prostate cancer in these individuals do not generally appear to be different than in sporadic cases. Interestingly, a study of 524 families with pathogenic germline *PALB2* alterations found no evidence for an increased risk of prostate cancer.

Carriers of the G84E mutation of the *HOXB13* gene also have a significantly higher risk for prostate cancer and are more likely to have early-onset familial disease. *HOXB13* mutations are more frequent among families of Scandinavian heritage.

Germline *BRCA1* and *BRCA2* mutations (associated with hereditary breast and/or ovarian cancer syndrome) occur in approximately 0.2% to 0.3% of the general population, with higher rates seen in certain racial/ethnic groups. These mutations have been associated with an increased risk for prostate cancer in numerous reports. In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in the risk for prostate cancer, whereas the association of *BRCA1* mutations and increased risks for prostate cancer are less consistent. Furthermore, prostate cancer in those with germline *BRCA* mutations appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in non-carrier patients. Among lethal prostate cancer cases, 60% of mutation carriers of *BRCA1/2* and *ATM* report a negative family history.

Interim results of the IMPACT study, which enrolled participants aged 40 to 69 years with germline *BRCA1/2* mutations (919 *BRCA1* carriers; 902 *BRCA2* carriers) and a control group with wild-type *BRCA1/2* who are related to mutation carriers (709 *BRCA1* non-carriers; 497 *BRCA2* non-carriers), were recently reported. All participants underwent annual PSA testing four times. Whereas no differences were seen between *BRCA1* carriers and non-carriers, the *BRCA2* carriers had a higher cancer incidence rate (19.4 per 1000 person years vs. 12.0; *P* = .03); were diagnosed at a younger age (61 vs. 64 years; *P* = .04); and were more likely to have clinically significant disease (77% vs. 40%; *P* = .01) than *BRCA2* non-carriers. One limitation of the study is that the biopsy compliance rate was higher in *BRCA2* carriers compared with non-carriers (73% vs. 60%). Further follow-up is required to assess the clinical utility of this early detection strategy.

The NCCN Prostate Cancer Early Detection Panel recommends inquiring about known personal or familial germline mutations associated with an elevated risk of cancer. If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended.

In addition, patients who meet hereditary risk assessment criteria established in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org) should be referred for genetic counseling/testing as appropriate. Commercial panels are now available to assess most of the main high-penetrance prostate cancer risk genes (*BRCA1*, *BRCA2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *HOXB13*, *CHEK2*, *NBN*, *PALB2*, *RAD51D*, and *TP53*). Information regarding the status of high-risk germline mutations should be used as part of the discussion about prostate cancer early...
This racial disparity is generally attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Although there are data suggesting a role for heritable genes linked to African ancestry, it is not known with certainty whether genetics rather than access to health care and other social determinants of health (eg, environmental exposures; patient and physician behaviors; delays in diagnosis; suboptimal treatment) are the main drivers of increased risk in this patient population.  

Prostate cancer screening has been best studied in Caucasians; data on screening in diverse and high-risk populations are lacking. In the PLCO trial, approximately 4.4% of the participants were African-American and 6.9% had a positive family history, but no subset analyses were performed. In the ERSPC trial, no information on ancestry or family history was reported.

**Recommendations for Early Detection in High-Risk Populations**

In conclusion, African-Americans, individuals with a family history of prostate cancer, and those with a known genetic predisposition represent high-risk groups. The panel believes that current data are insufficient to definitively inform the best strategy for prostate cancer early detection in these populations, and also notes that a baseline PSA value is a stronger predictive factor than a positive family history (as defined in the Guidelines above) or ancestry. Recent information, however, suggests that screening high-risk groups, including those of low socioeconomic status, is of benefit.

Overall, prostate cancer early detection is recommended at age 40 for BRCA2 carriers, and it is reasonable for individuals with other germline mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. In addition, the panel believes that individuals
with a family history of prostate cancer (defined as brother or father or multiple family members who were diagnosed with prostate cancer [but not clinically localized Grade Group 1] at <60 years of age or who died from prostate cancer) should begin shared decision-making about PSA screening at the age corresponding to 10 years prior to the age of the youngest family diagnosis. The panel also believes that it is reasonable for African-American individuals to begin shared decision-making about PSA screening at age 40 and to consider screening at annual rather than less frequent screening intervals. However, no current evidence shows that testing individuals of African descent at an earlier age will result in decreased morbidity and mortality compared to testing at age 45.

**Further Evaluation and Indications for Biopsy**

The previously cited RCTs used PSA thresholds to prompt a biopsy. PSA cut-points for biopsy varied somewhat between centers and trials over time. Although a serum PSA of 2.5 ng/mL has been used by many, a level of 3 ng/mL is supported by the trials and would more robustly limit the risk of overdetection. A higher threshold of 4 ng/mL is recommended for patients who choose to continue PSA screening past the age of 75 years. However, some panel members did not recommend limiting the option of biopsy to pre-specified PSA thresholds, noting that there are many other factors (eg, age, ancestry, family history, PSA kinetics) that should also inform the decision to perform biopsy.

The panel does not believe that DRE alone should be an absolute indication for biopsy in individuals with low PSA. The PPV of DRE in those with low PSA is poor (see DRE, above). However, a DRE that is very suspicious for cancer, independent of PSA, could be an indication of high-grade cancer in individuals with normal PSA values, and therefore biopsy can be considered. Clinical judgment should be used.

**Pre-Biopsy Workup**

The panel recommends that any individual with a PSA >3 ng/mL undergo workup for benign disease, a repeat PSA, and a DRE (if not performed during initial risk assessment) to inform decisions about whether to proceed with transrectal ultrasound (TRUS)-guided biopsy or additional testing with other biomarkers and/or multiparametric MRI. The panel recommends that multiparametric MRI should precede biopsy, if available. Biomarkers that improve the specificity of screening should be considered before biopsy. The roles of imaging and biomarker testing to inform biopsy decisions are discussed in detail below. The predictive value of biomarkers has not been correlated consistently with that of multiparametric MRI. Therefore, it is not known with certainty how such tests could be applied in optimal combination.

An abnormal DRE in this setting of elevated PSA has a high predictive value and the panel strongly recommends biopsy in these individuals.

Individuals who do not undergo a TRUS-guided biopsy should be followed up in 6 to 12 months with PSA and DRE. Patients with a persistent and significant increase in PSA should be encouraged to undergo biopsy.

**Risk Calculators**

Prostate cancer risk calculators have been developed to estimate an individual’s risk for prostate cancer from multiple factors. Common calculators are the Sunnybrook-, ERSPC-, and PCPT-based risk calculators. These online tools combine clinical variables—including but not limited to age, family history, ancestry, DRE, and PSA—to estimate both the risk for biopsy-detectable prostate cancer and the risk for biopsy-detectable high-grade prostate cancer. Such information potentially allows for more informed decision-making. However, such calculators have not been assessed in RCTs, and cut-points of risk associated with reductions in prostate cancer mortality remain unknown.
Such calculators have as much value in determining who might not need biopsy as in identifying those at higher risk. At this time, the panel does not recommend the use of risk calculators alone to determine whether biopsy is indicated. Clinical judgment and patient preferences need to be taken into consideration.

**Magnetic Resonance Imaging**

Considerable interest exists in using multiparametric MRI both pre-biopsy to select patients for biopsy and during biopsy to guide needle placement. The goals of using multiparametric MRI in these settings include reducing the number of individuals undergoing biopsy, reducing the detection of indolent disease (and thus the risks of overtreatment and overtreatment), and improving the detection of clinically significant disease through targeted biopsies.

MRI has generally been shown to have superior sensitivity for clinically significant prostate cancer when compared to TRUS biopsy. In the multicenter, paired-cohort PROMIS study, 576 participants with no prior biopsy and elevated PSA <15 ng/mL underwent multiparametric MRI followed by TRUS biopsy and perineal template mapping biopsy. Clinically significant cancer (Grade Group ≥3 or a maximum cancer core length ≥6 mm by template mapping biopsy) was found in 40% of patients. In detecting clinically significant prostate cancer (some may question the cut-point of ≥6 mm used), MRI was more sensitive (93%; 95% CI, 88%–96%) than TRUS biopsy (48%; 95% CI, 42%–55%; P < .0001), but less specific (41%; 95% CI, 36%–46% for MRI vs. 96%; 94%–98% for TRUS-biopsy; P < .0001). If a normal MRI had been used to screen individuals for biopsy, 27% would have avoided biopsy. It is important to note that patients in this study did not undergo MRI-targeted biopsy, so the study does not provide direct evidence about the performance of MRI-guided biopsy.

An approach utilizing MRI prior to biopsy followed by MRI-guided biopsy was directly compared to conventional TRUS biopsy in the PRECISION trial. PRECISION was a randomized, non-inferiority trial conducted in 25 centers across 11 countries. A total of 500 participants were randomized to either MRI (with or without targeted biopsy) or a 10- to 12-core TRUS biopsy. In the MRI arm, 28% avoided biopsy based on a normal MRI (Prostate Imaging Reporting and Data System [PI-RADS] <3). Clinically significant prostate cancer was detected in 38% in the MRI group and in 26% in the standard biopsy group. Thirteen percent fewer participants in the MRI group received a diagnosis of low-risk disease. Because PRECISION was conducted primarily in Europe at centers of excellence in prostate MRI, the generalizability of some of its findings remain unproven.

The finding that MRI before biopsy reduces negative biopsies and detection of indolent disease has been substantiated in numerous studies in both the initial and repeat biopsy settings.
methods of targeted biopsy (cognitive and fusion), and MRIs were read locally. Still, generalizability questions remain because all study centers had experience with prostate MRI and targeted biopsy, two centers enrolled 36% of all patients, and interobserver agreement in MRI interpretation was not addressed.

A similar prospective, multicenter comparative effectiveness study included 626 biopsy-naïve patients at four centers in the Netherlands: the 4M study. All patients underwent pre-biopsy MRI followed by systematic biopsy. Those with abnormal MRI also underwent in-bore MRI-guided biopsy. All MRIs were centrally reviewed by two highly experienced radiologists who were experts in prostate MRI. Overall, 49% of MRIs were read as normal (PI-RADS 1–2) and only 6% as indeterminate (PI-RADS 3). Clinically significant cancer (Grade Group ≥2) was detected in 30% of participants using the combined approach, in 25% using the MRI-targeted approach, and in 23% using a systematic approach. No difference in clinically significant prostate cancer detection was seen between targeted and systematic biopsy (difference, 2%; 95% CI, -1–5). Similar to PRECISION and MRI-FIRST, detection of insignificant cancer was lower using the targeted approach (difference, 11%; 95% CI, 7–14). Not biopsying those with PI-RADS 1–2 MRI missed only 4% of those with clinically significant prostate cancer detected on systematic biopsy. Among the 317 individuals with an abnormal MRI, 21 (7%) had cancer detected only on systematic biopsy. This study is remarkable for the high proportion of individuals (49%) who could have avoided biopsy based on a normal MRI while still maintaining an equivalent detection of clinically significant prostate cancer when compared to systematic biopsy for all individuals. Like MRI-FIRST and multiple retrospective studies, this study also shows that a relatively small proportion of clinically significant prostate cancer would be missed by omitting systematic biopsy. The authors acknowledge that this study represents the best-case scenario where MRI is performed and interpreted by experts and targeted biopsy is performed by experts.

The results may not be widely generalizable without extensive training of radiologists and urologists, but the potential for the MRI-targeted approach is relatively high for achieving the goals of reducing biopsies, maximizing detection of clinically significant prostate cancer, and reducing overdetection of indolent cancer.

In the Trio study, 2103 patients with prostate lesions visible by MRI underwent both MRI-targeted and systematic biopsy. The primary outcome measure was cancer detection according to Grade Group. The rate of detection of Grade Group 1 cancers was significantly lower by MRI-targeted biopsy than by systematic biopsy, whereas, the rate of detection of Grade Group ≥3 cancer was significantly higher with MRI-targeted biopsy (P < .01 for all comparisons). Of the 404 participants who underwent subsequent radical prostatectomy, upgrading to Grade Group ≥3 cancer occurred in 16.8% based on systematic biopsy, 8.7% based on MRI-targeted biopsy, and 3.5% based on the combination. The combined approach also resulted in 59 additional cancer diagnoses of Grade Group ≥3 than would have found by use of either method alone.

The Canadian multicenter, prospective randomized PRECISE clinical trial included 453 biopsy-naïve patients with a clinical suspicion of prostate cancer and PSA ≤20 ng/mL. Participants were randomized to undergo MRI followed by targeted biopsy only if PI-RADS score was 3 or higher (MRI-TB) or systematic TRUS biopsy. The primary outcome measure, the proportion of men with a diagnosis of Grade Group 2 or greater cancer, was similar in the two groups (35% vs. 30%, respectively; absolute difference, 5%; 97.5% 1-sided CI, -3.4% to infinity; noninferiority margin, -5%). Thus, the MRI-TB approach was non-inferior to the systematic TRUS biopsy approach. Importantly, 37% of participants in the MRI-TB group had a negative MRI and avoided biopsy, adverse events were less common in the MRI-TB group, and the detection of Grade Group 1 cancer...
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was lower in the MRI-TB group (22% vs. 10%; risk difference, -11.6%; 95% CI, -18.2% to -4.9%).

Many other studies support this notion and also note that fewer significant upgrades are seen at radical prostatectomy in those who underwent initial biopsy using MRI targeting. However, evidence from other studies is mixed as to whether MRI-guided biopsy improves clinically significant prostate cancer detection in individuals without a prior biopsy. For example, a single-center trial randomized 130 biopsy-naïve individuals to a control group that received TRUS-guided random biopsy alone or to a group that received pre-biopsy multiparametric MRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion-targeted biopsy. Similar rates of detection of prostate cancer (64% vs. 57%; P = .5) and of clinically significant cancer (55% vs. 45%; P = .8) were seen in the two arms. In another randomized trial, 212 biopsy-naïve patients with suspected prostate cancer were assigned to a pre-biopsy multiparametric MRI group or a standard biopsy group. Participants in the multiparametric MRI group had targeted fusion biopsies if suspicious lesions were seen. Otherwise, they received standard biopsies. More clinically significant prostate cancers were detected in the multiparametric MRI arm (43.9% vs. 18.1%; P < .001).

Similar to the studies above, multiple retrospective studies have shown that adding MRI-targeted biopsy to systematic biopsy increases the yield of clinically significant prostate cancer over systematic biopsy alone. A 2019 Cochrane systematic review identified 18 cross-sectional studies that compared template-guided biopsy with MRI only, MRI-targeted biopsy, MRI with or without MRI-targeted biopsy, and/or systematic biopsy for the detection of Grade Group ≥2 prostate cancer. The authors concluded that MRI with or without MRI-targeted biopsy detects a greater number of significant cancer while detecting fewer insignificant cancers compared with systematic biopsy. Another systematic review suggests that the approach of MRI first in biopsy-naïve individuals may improve detection of clinically significant cancer, reduce the number of biopsy cores per procedure, reduce adverse effects, and potentially reduce unnecessary biopsies.

The PI-RADS from the American College of Radiology gives recommendations for high-quality MRI in prostate cancer care, including recommendations related to the use of MRI to direct targeted biopsies. In addition, the European Society of Urogenital Radiology established guidelines for optimal multiparametric MRI of the prostate, including for detection and targeted biopsies. The vast majority of published evidence using MRI for prostate cancer diagnosis comes from high-volume centers of excellence. The generalizability of these findings is not yet clear. Overall, in light of evidence showing considerable interobserver variability in the interpretation of prostate MRI, the panel emphasizes the need for high-quality MRI and for radiologic expertise for optimal reading of scans.

At this time, the panel believes that the multiparametric MRI should be considered prior to TRUS-guided biopsy to inform biopsy decisions and to help identify regions of the prostate that may harbor cancer. However, the panel cautions that false negatives can occur and proceeding to TRUS-guided biopsy should still be considered, particularly in situations where the patient is considered to be at high risk for cancer based on PSA density (PSAD) or other biomarkers.

The panel recommends that MRI should precede biopsy, if available, and that image-guided biopsy techniques should be employed routinely (see Targeted Biopsy Techniques, below). Although some advocate for excluding systematic biopsy in those undergoing MRI targeting, most advocate for a combined approach as some high-grade cancers are uniquely detected using the systematic approach. The panel cautions that some significant cancers exist outside targets identified on MRI,
considerable inter-reader variability exists among radiologists interpreting MRI.\textsuperscript{215,216} More information is needed about the generalizability of findings from the trials mentioned above, and cost-effectiveness of pre-biopsy MRI in the United States has not been demonstrated.

In cases of individuals with at least one negative biopsy, the panel believes that multiparametric MRI may help identify regions of cancer missed on prior biopsies; it should therefore be considered in this setting (also see \textit{Repeat Biopsies}, below).\textsuperscript{217} Because the negative predictive value (NPV) of a normal MRI varies, some may combine other biomarkers (discussed below) or even PSAD before choosing not to perform a biopsy in individuals with an elevated PSA and a normal MRI.

**Biomarker Testing: PSA Derivatives and Other Tests**

When the first recommendations for early detection programs for prostate cancer were made, serum tPSA was the only PSA-based test available. PSA derivatives and other assays exist that potentially improve the specificity of testing and thus may diminish the probability of unnecessary biopsies.

When a patient meets the standards for biopsy, sometimes the patient and physicians wish to further define the risk of cancer before proceeding to biopsy with its associated risks (see \textit{Risks of Biopsy}, below). Several biomarker tests have been developed with the goals of refining patient selection for biopsies, decreasing unnecessary biopsies, and increasing the specificity of cancer detection, without missing a substantial number of higher-grade (Grade group \(\geq 2\)) cancers. These tests may be especially useful in individuals with PSA levels between 3 and 10 ng/mL. Most often, these tests have been used in patients who have had one negative biopsy to determine if repeat biopsy is an appropriate consideration.

The panel recommends consideration of biomarker tests that have been validated in peer-reviewed, multi-site studies using an independent cohort of patients. These include percent free PSA (%f PSA), which may improve cancer detection and Prostate Health Index (PHI), SelectMDx, 4Kscore\textsuperscript{®}, or ExoDx Prostate Test (EPI), which may further define the probability of Grade Group \(\geq 2\) cancer in patients with PSA levels \(>3\) ng/mL who have not yet had a biopsy. %f PSA, PHI, 4Kscore, EPI, PCA3, and ConfirmMDx may also be considered for those who have had at least one prior negative biopsy and are thought to be at higher risk. The extent of validation of these tests across diverse populations varies (see below). Results of biomarker assays can be complex and should be interpreted with caution. Referral to a specialist should be considered. It should be pointed out that multiparametric MRI is also a consideration in these same patients. It is not yet known, with certainty, how biomarker tests can be applied in optimal combination with MRI.

Head-to-head comparisons have been performed for some of these tests, used independently or in combinations in the initial or repeat biopsy settings, but sample sizes were often small and results varied.\textsuperscript{218-230} Therefore, the panel believes that no biomarker test can be recommended over any other at this time. Furthermore, a biomarker assay can be done alone or in addition to multiparametric MRI/refined biopsy techniques.\textsuperscript{231,232} The optimal order of biomarker tests and imaging is unknown; and it remains unclear how to interpret results of multiple tests in individual patients—especially when results are contradictory. However, several recent studies suggest that upfront biomarker testing with conditional MRI may be an efficient and effective way to assess those with a persistently elevated PSA.\textsuperscript{232-234}

Results of any of these tests, when performed, should be included in discussions between the clinician and patient to assist in decisions regarding whether to proceed with biopsy. These and other tests are discussed below.
Age- and Ancestry-Specific PSA Reference Ranges

Age-specific PSA reference ranges were introduced by Oesterling and colleagues as a method to increase cancer detection (ie, increase sensitivity) in younger individuals by lowering PSA cutoffs for biopsy and to decrease unnecessary biopsies (ie, improve specificity) in older individuals by increasing PSA cutoffs. Several groups have investigated these age-specific ranges with equivocal results. Others have suggested specific reference ranges for men of African descent. However, the exact roles of these age- and ancestry-specific PSA cutoffs in the early detection of prostate cancer remain unclear. The panel has no recommendations regarding routine use of these ranges.

PSAV

The rate of change in PSA over time is broadly termed PSA velocity (PSAV), determined by at least three separate PSA values calculated over at least an 18-month period. Carter and colleagues first showed that PSAV is greater in individuals eventually diagnosed with prostate cancer than in those not diagnosed with the disease and suggested its use as a screening tool. In a subsequent study of 980 participants enrolled in the BLSA, Carter and colleagues explicitly linked PSAV with the risk of prostate cancer death by observing that PSAV recorded 10 to 15 years before cancer diagnosis (commonly with PSA <4 ng/mL) was associated with disease-specific survival up to 25 years later. The relative risk of prostate cancer death was higher in those with PSAV >0.35 ng/mL/y compared to those with PSAV ≤0.35 ng/mL/y (RR, 4.7; 95% CI, 1.3–16.5; P = .02). These data provide support that PSAV may help identify lethal cases. However, the small number of deaths from prostate cancer (20) precludes definitive conclusions.

In two other studies of patients with prostate cancer, very high PSAV (>2 ng/mL/y) during the year before diagnosis was associated with a greatly increased risk of death from the disease, but this is a much higher cutoff for PSAV than the one proposed by Carter and colleagues.

Vickers and colleagues, however, have questioned the role of PSAV in tumor detection among individuals with low PSA levels. The analysis was performed on 5519 participants undergoing biopsy regardless of indication in the control arm of the PCPT to explore the additional yield from a PSAV threshold of 0.35 ng/mL/y. The main finding of this study was that PSAV did not significantly increase the predictive accuracy of high PSA levels or positive DRE and might substantially increase the number of individuals recommended for biopsy. However, these findings should be applied only to individuals similar to those studied in PCPT (≥55 years of age; 96% Caucasian-American; 17% family history of prostate cancer; PSA values ≤3 at enrollment). A recent analysis of PSAV in 1634 participants of the IMPACT study found that PSAV did not predict biopsy results any better than PSA levels alone in those with PSA >3.0 ng/mL. However, in a study of individuals pursuing a second biopsy after an initial negative biopsy, PSAV was an independent predictor of overall prostate cancer, intermediate-grade cancer, and high-grade cancer.

Panelists disagree as to the value of PSAV alone as a criterion for considering biopsy when the PSA level is low (<2.0 ng/mL). Due to its potential capacity to identify tumors with lethal potential, most panelists agree that PSAV (PSAV ≥0.35 ng/mL/y) is only one criterion to consider when deciding whether to perform biopsy for individuals with low PSA levels. Panelists do not agree as to the threshold of PSAV that should prompt consideration of biopsy, but agree that high PSAV alone, at low PSA levels, does not mandate biopsy, but rather should aid in the
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decision-making process. Other factors such as age, comorbidity, ancestry, and family history also should be considered.

Panelists would also like to draw attention to the following caveats: the predictive value of PSAV can be influenced by PSA level;\(^{63,241,246}\) PSAV is not useful in patients with very high (>10 ng/mL) PSA values;\(^{247}\) PSAV measurements can be confounded by prostatitis, a condition that can cause dramatic and abrupt increases in PSA levels;\(^{248}\) and fluctuations among measurements can occur as a result of either laboratory inter-assay variability related to the use of different commercially available sources or individual biological variability. Thus, an abnormal PSA result should be confirmed by retesting.

%f PSA

Unbound or free PSA (fPSA), expressed as a ratio of tPSA, is a clinically useful molecular form of PSA, with the potential to improve early detection, staging, and monitoring of prostate cancer. Several molecular forms of PSA are known to circulate in the blood. In most individuals, the majority (60%–90%) of circulating PSA is covalently bound to endogenous protease inhibitors. Most immunoreactive PSA is bound to the protease inhibitor alpha-1-antichymotrypsin. Other immunoreactive PSA-protease inhibitor complexes, such as alpha-1-antitrypsin and protease C inhibitor, exist at such low serum concentrations that their clinical significance has not been determined. In addition, a large proportion of PSA is complexed with alpha-2-macroglobulin (AMG). Unfortunately, this PSA-AMG complex cannot be measured by conventional assays because of the shielding (or "caging") of PSA antigenic epitopes by AMG.

Most clinical work investigating the use of the molecular forms of PSA for early detection of prostate cancer has focused on the percentage of PSA found circulating in the free or unbound form. Numerous studies have shown that the %f PSA is significantly lower in patients who have prostate cancer compared with those who do not.

The FDA approved the use of %f PSA for the early detection of prostate cancer in men aged \(\geq\)50 years with a non-suspicious DRE and PSA levels between 4 ng/mL and 10 ng/mL (PSA levels where most secondary testing is done). The multi-institutional study that characterized the clinical utility of this assay showed that a 25% fPSA cutoff detected 95% of prostate cancers while avoiding 20% of unnecessary prostate biopsies.\(^{249}\)

Since its approval by the FDA, testing for %f PSA has gained widespread clinical acceptance in the United States, specifically for patients with normal DREs who have previously undergone prostate biopsy because they had a tPSA level within the "diagnostic gray zone."

cPSA

PSA exists in free and several complexed forms. Direct measurement of the complexed form with alpha-1-antichymotrypsin is now available. For practical purposes, tPSA consists essentially of fPSA and the alpha-1-antichymotrypsin complexed form (cPSA). The threshold levels are therefore not equivalent; cPSA levels of 2.2 ng/mL and 3.4 ng/mL are equivalent to tPSA levels of 2.5 ng/mL and 4.0 ng/mL, respectively. In a multicenter trial of 831 participants, of whom 313 had prostate cancer, researchers found that cPSA in the range of 80% to 95% sensitivity thresholds increased specificity compared with tPSA.\(^{250}\) Results were similar for %cPSA and %fPSA.

Therefore, the ratio of cPSA to tPSA should provide information comparable to the fPSA to tPSA ratio.\(^{251}\) Other studies also demonstrated an enhanced specificity of cPSA within certain tPSA ranges.\(^{252-254}\) Use of cPSA has been approved as an aid in the detection of prostate cancer in individuals aged 50 years or older in conjunction with DRE. However,
because cPSA has not gained widespread acceptance in day-to-day clinical practice, it has not been incorporated into these algorithms.

**PSAD**

PSAD requires the measurement of prostate volume by TRUS and is expressed as the PSA value (in ng/mL) divided by prostate volume (in cc).

PSAD is a means of discriminating prostate cancer from BPH: the lower the PSAD, the greater the probability of BPH. Thus, PSAD potentially identifies individuals who do not have prostate cancer but have high PSA secondary to large-volume prostates. A PSAD cutoff of 0.15 ng/mL/cc was recommended in earlier studies, which spared as many as 50% of individuals from unnecessary biopsies. However, some subsequent studies have reported that the 0.15 cutoff has insufficient sensitivity.

More recent studies have tried to improve upon the performance of PSAD by using cPSA or fPSA in the numerator or correcting the denominator for transition zone volume. The clinical utility of these methodologies remains unclear.

PSAD has also been shown to correlate with prostate cancer presence and aggressiveness, and may predict adverse pathology and biochemical progression after treatment.

The lack of precision of measurement of both PSA and prostate volume has prevented the widespread clinical acceptance of PSAD. In addition, studies have shown that %f PSA provides results comparable to PSAD in early-detection algorithms.

While the panel recognizes that PSAD may explain an elevated PSA value considered after negative biopsies, it has not incorporated PSAD into the early detection guidelines as a baseline measure, because PSAD alone may offer little added benefit over other tests and requires ultrasound. Still, the panel agrees that PSAD has been clinically underutilized and may be considered in evaluating patients, especially those who have had prior US-determined measurements of prostate volume.

**PCA3**

PCA3 is a noncoding, prostate tissue-specific RNA that is overexpressed in prostate cancer. Current assays quantify PCA3 overexpression in post-DRE urine specimens. PCA3 appears most useful in determining which patients should undergo a repeat biopsy. For example, in a prospective multicenter clinical study of 466 individuals with at least one prior negative prostate biopsy, a PCA3 score cutoff of 25 showed a sensitivity of 78%, specificity of 57%, NPV of 90%, and PPV of 34%. Participants with a score of ≥25 were 4.6 times more likely to have a positive repeat biopsy than those with a score <25.

Results were reported from an NCI Early Detection Research Network (EDRN) validation study of the PCA3 urinary assay in 859 individuals scheduled for a diagnostic prostate biopsy in 11 centers. The primary outcomes were reported at a PPV of 80% (95% CI, 72%–86%) in the initial biopsy setting and an NPV of 88% (95% CI, 81%–93%) in the repeat biopsy setting. Based on the data, use of PCA3 in the repeat biopsy setting would reduce the number of biopsies by almost half, and 3% of those with a low PCA3 score would have high-grade prostate cancer that would be missed. In contrast, the risk of high-grade disease in those without prior biopsy with a low PCA3 is 13%. Thus, the panel believes that this test is not appropriate to use in the initial biopsy setting.

The FDA has approved the PCA3 assay to help decide, along with other factors, whether a repeat biopsy in men aged 50 years or older with one or more previous negative prostate biopsies is necessary. This assay is recommended for those with a previous negative biopsy in order to avoid repeat biopsy by the Molecular Diagnostic Services Program (MolDX) and
The PHI is a combination of the tPSA, fPSA, and proPSA tests. In a multicenter study, it was noted to have approximately double the sensitivity of fPSA/tPSA for cancer detection in those with serum PSA concentrations between 2 and 10 ng/mL. In addition, the PHI correlated with cancer grade and had an AUC of 0.72 for discrimination of high-grade (Grade Group ≥2) cancer from low-grade cancer or negative biopsy. Another prospective cohort study calculated an AUC of 0.815 for the detection of high-grade (Grade Group ≥2) prostate cancer. This study determined the optimal cutoff of PHI to be a score of 24, which should lead to 36% of biopsies avoided with approximately 2.5% of high-grade cancers missed. Other studies have also shown that PHI can predict aggressive prostate cancer and has potential clinical utility.

The PHI was approved by the FDA in 2012 for use in those with serum PSA values between 4 and 10 ng/mL. A clinical utility study conducted at four large urology group practices showed that use of PHI was in fact associated with a decrease in biopsy procedures performed when compared to historical controls from the same physicians (36.4% vs. 60.3%; \( P < .0001 \)). Patients in the study had normal DRE and PSA values ranging from 4 to 10 ng/mL. Physician survey results showed that PHI results impacted biopsy decisions in 73% of cases. However, the authors of this study did not report the numbers of high-grade cancers missed, and some have estimated that it may be as high as 30%.

The 4Kscore test is another combination test that measures fPSA, tPSA, human kallikrein 2 (hK2), and intact PSA and also considers age, DRE results, and prior biopsy status. This test reports the percent likelihood of finding high-grade (Grade Group ≥2) cancer on biopsy. A prospective multi-institutional U.S. trial of 1012 patients showed that 4Kscore results have a high discrimination value (AUC, 0.82). In this study, using a threshold for biopsy of ≥15% risk allowed for 591 biopsies to be avoided (58%), while 183 high-grade tumors were detected and 48 high-grade tumors (4.7% of the 1012 participants) were missed. When 4Kscore was examined in 6129 participants in another prospective study, the AUC was also 0.82 (95% CI, 0.80–0.84). Using a 6% risk of high-grade cancer as a cutoff, 428 of 1000 individuals could avoid biopsy, with 119 of 133 high-grade cancers detected and 14 of 133 missed. A multicenter clinical utility study found a 65% reduction in prostate biopsies with use of the 4Kscore test. In addition, a correlation between 4Kscore risk category and Gleason score was seen (\( P < .01 \)). A meta-analysis that included 12 clinical validation studies (11,134 patients) led to a calculated pooled AUC for discrimination of Grade Group ≥2 prostate cancer of 0.81 (fixed effects 95% CI, 0.80–0.83).

The panel consensus is that the test can be considered for patients prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk for clinically significant prostate cancer. It is important for patients and their urologists to understand, however, that no optimal cutoff threshold has been established for the 4Kscore. If a 4Kscore test is performed, the patient and his urologist should discuss the results to decide whether to proceed with a biopsy.

ConfirmMDx

ConfirmMDx is a tissue-based, multiplex epigenetic assay that aims to improve the stratification of individuals being considered for repeat prostate biopsy. Hypermethylation of the promoter regions of \( GSTP1 \), \( APC \), and \( RASSF1 \) is assessed in core biopsy tissue samples. The test, performed in one CLIA-certified laboratory, is not FDA approved.
The European MATLOC study blindly tested this assay in archived tissue from 498 patients with negative biopsies who had repeat biopsies within 30 months. The NPV was 90% (95% CI, 87%–93%). In a multivariate analysis, ConfirmMDx was predictive of patient outcome (OR, 3.17; 95% CI, 1.81–5.53). A similar validation study was performed in the United States using archived tissue from 350 patients with negative biopsies who had repeat biopsies within 24 months. The NPV was 88% (95% CI, 85%–91%), and the test was again found to be predictive of outcomes on multivariate analysis (OR, 2.69; 95% CI, 1.60–4.51).

The panel believes that ConfirmMDx can be considered as an option for individuals contemplating repeat biopsy, because the assay may identify individuals at higher risk of prostate cancer diagnosis on repeat biopsy. This assay is approved for limited coverage by MolDX for the reduction of unnecessary repeat prostate biopsies.

**ExoDx Prostate(IntelliScore)**

ExoDx Prostate(IntelliScore), also called EPI, evaluates a urine-based 3-gene exosome expression assay utilizing PCA3 and ERG (V-ets erythroblastosis virus E26 oncogene homologs) RNA from urine, normalized to SPDEF (SAM pointed domain-containing ETS transcription factor). The background for these markers is supported by a number of studies, but the application to exosome detection is unique. This gene panel proposes to discriminate Grade Group ≥2 prostate cancer from Grade Group 1 and benign disease at initial biopsy. The population for which use of the assay was intended includes patients older than 50 years with no prior biopsy and a PSA value between 2 and 10 ng/mL. In a recent study by McKiernan et al, estimates of the AUC were similar in the training (0.74) and validation (0.71) cohorts for the assay, with significant improvements when the test was added to standard-of-care variables alone. Applying a cutoff value from the training cohort to serve as a threshold for biopsy in the validation cohort decreased the need for biopsy by 27% (138 of 519) while missing 8% (12 of 148) of Grade Group ≥2 cancers. The investigators propose this assay as a secondary or reflex test for risk stratification in conjunction with PSA screening. In the McKiernan study, the algorithm was validated in a test set of 255 patients and then validated in the extended screening validation cohort of 519 patients. The majority of exclusions were for urine volume >49 mL, assay failure, and application outside the intended use population.

A second independent validation study was a 2-phase adaptive clinical utility study that included 503 biopsy-naive patients with PSA levels between 2 and 10 ng/mL and compared EPI and biopsy results. In the first phase of this study, the AUC was 0.70 for predicting Grade Group ≥2 cancer by EPI. Using the validated cut-point 15.6, the test has an NPV of 89%, reducing total biopsies by 20% and missing 7% of Grade Group ≥2 cancer. The second phase of this trial will be reported in the future.

The panel believes that EPI can be considered as an option for individuals contemplating initial or repeat biopsy.

**SelectMDx**

SelectMDx is a gene expression assay performed on post-DRE urine that measures DLX1 and HOXC6 expression against KLK3 as internal reference. DLX1 and HOXC6 have been associated with prostate cancer aggressiveness. As with other assays, SelectMDx is designed to improve the identification of individuals with clinically significant prostate cancer prior to biopsy, thereby reducing the number of unnecessary biopsies.

The assay was developed on an initial training set of 519 patients from two prospective multicenter studies and was then validated in a separate set of 386 patients from these trials. Using the expression of DLX1 and HOXC6 alone resulted in an AUC of 0.76, a sensitivity of 91%, a specificity of 36%, an NPV of 94%, and a PPV of 27% for the prediction of Grade...
Group ≥2 prostate cancer. When the gene expression was combined with PSA levels, PSAD, DRE results, previous negative prostate biopsies, age, and family history in a multimodal model, the overall AUC was 0.90 in the training set and 0.86 (95% CI, 0.80–0.92) in the validation set. A retrospective observational study compared results of SelectMDx with multiparametric MRI results in 172 patients who had multiparametric MRI because of persistent clinical suspicion of prostate cancer or for local staging after positive biopsy.292 The AUC of SelectMDx for the prediction of multiparametric MRI outcome was 0.83, whereas the AUC for PSA and PCA2 were 0.66 and 0.65, respectively.

A multicenter study used pre-biopsy urine samples from 1955 individuals to validate the assay with a training cohort and a validation cohort.293 The AUC was 0.85, the sensitivity was 93%, the specificity was 47%, and the NPV was 95% for detection of Grade Group ≥2 prostate cancer in the 916-patient validation cohort. When only those with PSA levels <10 ng/mL were included, the values were 0.82, 89%, 53%, and 95%, respectively.

Overall, the panel believes that SelectMDx score is potentially informative in patients who have never undergone biopsy, and it can therefore be considered in such individuals.

**Additional Biomarker Tests**

The list of assays with the potential to permit improved detection of Grade Group ≥2 prostate cancers as an adjuvant to PSA screening is growing rapidly. Below, several of these assays are discussed. Given the lack of validation of the models/algorithms in additional, independent publications, their unclear behavior in other screened populations, and the lack of clarity regarding the incremental value and cost-effectiveness of these assays, however, the panel cannot recommend their routine use at this time. Furthermore, potential sources of error in these approaches include undetected cancers, as high as 25%, in patients with a single negative prostate biopsy. Other significant and unaddressed issues include the well-known upgrading (32%–49%) that occurs in patients with Grade Group 1 cancer at biopsy at the time of pathologic assessment of the surgical specimen. Longer-term follow-up of the cohorts to determine whether missed prostate cancers were ultimately detected is needed. In addition, validation of these tests in other cohorts is needed before they can be accepted as alternatives to (or perhaps preferable to) other tests, described above.

**Mi-Prostate Score**

The Mi-Prostate Score (MiPS) assay measures total serum PSA and post-DRE urine expression of PCA3 and the TMPRSS2:ERG fusion gene.294 Rearrangements of the ERG gene are found in approximately half of prostate cancers.295 The TMPRSS2:ERG fusion specifically occurs at high frequency and appears to be an early event in prostate cancer development.296 The role of PCA3 in prostate cancer is discussed above. Early studies suggested that the combination of these two markers improved the prediction of prostate cancer on biopsy.297

A MiPS validation study included 1244 individuals with planned biopsy (80% with no prior prostate biopsy) in a validation cohort.294 The AUC for the prediction of any cancer was 0.751 for MiPS, compared with 0.585 for PSA alone. For the prediction of Grade Group ≥2 cancer, the AUCs for MiPS and PSA alone were 0.772 and 0.651, respectively.

A multicenter prospective validation study of this assay included 516 participants in a development cohort and 561 participants in a validation cohort.298 In the validation cohort, use of the test improved specificity for the presence of Grade Group ≥2 cancer from 17% to 33%, with the sensitivity at 93%. The authors calculate that 42% of unnecessary biopsies could have been avoided by using the assay in biopsy decisions.
Based on reasons discussed above (see Additional Biomarker Tests), the panel considers MiPS to be investigational at the present time, but will review additional information as it becomes available.

**Sentinel PCa Test**
Recently, Wang and colleagues reported on the development and initial performance of a platform that interrogates small noncoding RNAs (sncRNA) isolated from urinary exosomes. The assay, Sentinel PCa Test, differentiates patients with prostate cancer from those with no evidence of prostate cancer. The test was developed on an initial cohort of 235 participants and validated using a case-control sample of 1436 subjects with a wide range of PSA values. Sensitivities and specificities for detection of high-grade cancer (Grade Group 2 or higher) were very high. This test awaits further validation, especially in the group of patients with negative DREs and PSAs in the range where most such tests are used (ie, 2.5 ng/mL – 10.0 ng/mL).

**Biopsy Technique**

**Initial Biopsy**
Transrectal or transperineal systematic prostate biopsy under TRUS guidance with or without targeting of lesions seen on pre-biopsy MRI is the recommended technique for prostate biopsy. When systematic biopsy is performed, the panel recommends an extended-pattern, at least 12-core biopsy (sexant medial and lateral peripheral zone and lesion-directed). This extended-pattern scheme has been validated and results in enhanced cancer detection compared to sextant biopsy schemes. Anteriorly directed biopsy is not supported in routine biopsy. However, this can be added to an extended biopsy protocol in a repeat biopsy if PSA is persistently elevated.

TRUS-guided biopsy can be performed via a transrectal or a transperineal approach. The PROMIS trial demonstrated improved detection of clinically significant cancer using transperineal template biopsy compared to transrectal biopsy. Transperineal biopsy may be associated with a lower risk of sepsis, and performance in a clinic setting under local anesthesia has been described. However, extensive perineal template biopsies may lead to higher rates of other complications such as urinary retention. A definitive study comparing a more limited transperineal biopsy versus conventional transrectal biopsy has not been performed. The panel views both approaches as reasonable options.

**Targeted Biopsy Techniques**
Interest in the use of novel imaging, particularly MRI, to guide needle placement during biopsy (see Magnetic Resonance Imaging, above) has recently increased.

Targeted biopsy techniques include cognitive or visual targeting (guiding with US, based on an MRI image), TRUS-MRI fusion platforms (merging a stored MRI image with a real-time US image), and direct in-bore magnetic resonance (MR)-guided biopsy (performed by an interventional radiologist while the patient is in the scanner). Data show that multiparametric MRI followed by lesion targeting increases the detection of clinically significant, higher-risk (Grade Group ≥3) disease while lowering the detection of low-risk (Grade Group 1) disease. Data also suggest that different targeting techniques detect clinically significant prostate cancer at similar rates.

Evidence from clinical trials and other studies evaluating MRI-targeted biopsy in the initial biopsy setting is described above (see Magnetic Resonance Imaging, above).

Overall, the panel believes that the data for the use of MRI and MRI-targeted biopsies in the initial biopsy setting are increasingly compelling. However, studies using both targeted and systematic sampling routinely demonstrate higher yield of clinically significant cancer with the combined...
approach and improved sensitivity. Therefore, a combination of systematic and targeted procedures is preferred when MRI-targeting capabilities are available, at least at initial biopsy.

Repeat Biopsies

A negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. If clinical suspicion of cancer persists after a negative biopsy, consideration can be given to the use of multiparametric MRI followed by an appropriate targeted biopsy technique based on the results. In addition, biomarker testing can also be considered in these individuals to inform decisions regarding repeat biopsy (see Biomarker Testing: PSA Derivatives and Other Tests, above).

Targeted Biopsy for Repeat Biopsy

After one or more negative TRUS biopsies, individuals who are considered at high risk (eg, those with persistently elevated or rising PSA) can be considered for MRI followed by targeted biopsy based on several studies showing improved detection of clinically significant prostate cancer in this setting. Reported cancer detection rates by targeted fusion biopsies in individuals with previous negative biopsies range from 34% to 51%. Studies that used direct MR guidance for targeted biopsies have reported similar cancer detection rates in those with previous negative biopsies: 41% to 56%.

The targeted biopsy approach may lead to a higher rate of detection of clinically significant cancer in individuals with prior negative biopsy than repeat systematic biopsies, which lead to the identification of more low-risk tumors. For instance, in one retrospective cohort study, 105 participants with prior negative biopsies and elevated PSA underwent multiparametric MRI followed by standard 12-core systematic biopsy and MR-US fusion-targeted biopsy regardless of MRI results. Prostate cancer was found in 36 individuals (34%). In this study, 21 of 23 cancers (91%) identified by targeted biopsy were significant (Grade Group 2 or mean core length ≥4 mm), compared with 15 of 28 cancers (54%) identified by standard biopsy. Targeted biopsies missed two cases of clinically significant cancer compared with five missed cases with standard biopsies.

Another prospective study included 347 patients with findings suspicious for prostate cancer, many of whom had one or more previous negative biopsies. All patients received a multiparametric MRI, and those with abnormal findings proceeded to MRI-TRUS fusion-targeted biopsies. The outcome was defined as improved detection in targeted cores, with significantly more cancer detected in targeted cores than in systematic biopsies (30% vs. 8.2%). About 12% of those without MRI-suspicious lesions were diagnosed with intermediate-risk tumors. In this study, the cancer detection rate was 51% in individuals with previous negative biopsies.

In a prospective study, 583 patients (56% with prior negative biopsy) underwent multiparametric MRI. All participants received systematic 12-core biopsies, and those with lesions seen on MRI also received fusion-guided biopsies. Multivariate analysis revealed that a higher MRI suspicious score increased the likelihood of finding Grade Group ≥2 cancer by 3.3-fold (95% CI, 2.2–5.1; P < .0001).

A recent meta-analysis of 16 studies (1926 individuals) also showed that MRI-targeted biopsy improved detection of clinically significant prostate cancer in those with previous negative biopsies over standard TRUS biopsy. Recently, the use of high-resolution micro-ultrasound has been compared to mpMRI and found to perform similarly for the detection of prostate cancer.

Overall, the panel believes that targeted biopsy techniques may help identify regions of cancer missed on prior biopsies and should be strongly
Saturation Biopsy Techniques

In saturation biopsies, cores are collected systematically every few millimeters across the entire prostate to improve prostate cancer detection over that of a standard 12-core biopsy. In one study, transperineal prostate mapping biopsy was used to calculate biopsy density (the ratio of the total number of specimens retrieved to prostate volume) in 436 patients to determine the optimal sampling approach. Results showed that biopsy density >1.5 was associated with a 1.5-fold higher rate of prostate cancer diagnosis and a higher rate of detection of higher volume Grade Group 1 disease.

Saturation biopsies can be performed via transrectal or transperineal approaches, the latter of which is often image-guided (see Targeted Biopsy Techniques for Repeat Biopsy, above). The transrectal and transperineal saturation approaches seem to have similar rates of cancer detection. In fact, one study compared the approaches head-to-head and found similar cancer detection rates in the repeat biopsy setting (31.4% for transrectal vs. 25.7% for transperineal; \( P = .3 \)). The transperineal approach may have a lower risk of infection, may allow for better saturation of the gland, and may be more acceptable to patients compared with the transrectal approach. In fact, recent studies reported zero or near-zero rates of sepsis in individuals biopsied with the transperineal approach. Another possible benefit of the transperineal over the transrectal approach is more accurate risk assessment (cancer volume and grade). However, the transperineal approach may be associated with a higher rate of urinary retention. The transrectal approach can be performed routinely in the office whereas transperineal biopsy often requires more extensive local or systemic analgesia.

A study of transperineal template-guided mapping biopsy found detection rates of 55.5%, 41.7%, and 34.4% for those with 1, 2, and ≥3 previous negative biopsies, respectively. Other groups have reported similar rates of detection using saturation biopsies in individuals with previous negative biopsies. Compared with an extended biopsy approach (12–14 cores), one prospective, non-randomized study found that transrectal saturation biopsy detected significantly more cancers in individuals with one previous negative biopsy (32.7% vs. 24.9%; \( P = .0075 \)). The detection of insignificant cancer did not differ significantly between the groups (40.1% vs. 32.6%; \( P = .2 \)).

Despite this emerging evidence, the panel does not recommend a saturation biopsy strategy for all individuals with previous negative biopsies at this time given the benefits seen for MRI and MRI-targeted biopsy in this patient population.

Risks of Biopsy

The problem of repeated biopsies is gaining attention in the PSA debate due to increasing concerns about the risks of complications, particularly drug-resistant Escherichia coli infections. The range of potential infectious complications includes urinary tract infection (UTI), epididymitis, orchitis, prostatitis, and sepsis. Other morbidities include rectal bleeding, hematuria, vasovagal episodes, fever, hematospermia, and dysuria.

In an analysis of 17,472 individuals in the SEER database, prostate biopsy was associated with a 2.7-fold increased risk of 30-day hospitalization. These investigators also reported that while the incidence of infectious complications following prostate biopsy has significantly increased in recent years, the incidence of noninfectious complications has remained relatively stable. These results are similar to those from a Canadian study of 75,190 participants who were biopsied, in which the hospitalization rate
increased from 1.0% in 1996 to 4.1% in 2005. About 70% of all admissions were related to infections. A recent analysis of the PLCO trial, however, observed that biopsy complications were infrequent and that biopsy was not associated with a higher risk of mortality.

Fluoroquinolones, particularly ciprofloxacin, are commonly used as a prophylaxis for TRUS biopsy. Recent studies have reported that about half of post-biopsy infections are resistant to fluoroquinolone, many of which are also resistant to other antibiotics. Resistance is associated with prior prophylactic exposure to fluoroquinolone. The FDA labels for drugs in this class include additional warnings about disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system; risk of ruptures or tears in the aorta blood vessel; serious low blood sugar levels; and mental health side effects. The American Urological Association recommends that exposure to fluoroquinolones be limited to no more than 24 hours when used in conjunction with transrectal prostate biopsy.

Although these fluoroquinolones-resistant infections will respond to cephalosporins, measures are needed to prevent additional resistant strains. One strategy is to develop more stringent criteria for biopsy. Other proposed strategies include transperineal prostate biopsy, selectively targeted antibiotic prophylaxis with pre-biopsy rectal culture, and selectively augmented prophylaxis with two antibiotics in higher risk patients. Results from a randomized study suggest that prophylactic, single-dose gentamicin may be an effective alternative to fluoroquinolones.

Up to 90% of individuals undergoing a prostate biopsy have reported some discomfort during the procedure. Both topical lidocaine gel and an injectable nerve block have been shown to be safe and efficacious for reducing discomfort. Topical lidocaine was more efficacious in reducing pain during probe insertion, whereas peri-prostatic injection reduced pain during the biopsy itself. Results of one small clinical trial suggest that a combination of lidocaine suppository and periprostatic nerve block might be more effective at reducing pain during prostate biopsy than either one alone. Another small trial found the combination of lidocaine with pelvic plexus block to be most effective at relieving pain associated with prostate biopsy. More recently, a randomized trial compared peri-prostatic nerve block with subcutaneous perineal anesthesia and intrarectal lidocaine gel with total intravenous anesthesia in 216 patients receiving a TRUS-guided transperineal prostate biopsy. The combination treatment resulted in less pain during the biopsy, shorter operation times ($P < .05$), more stable hemodynamics and respiratory status, and fewer surgical complications ($P < .05$).

These minor anesthetic techniques greatly enhance the acceptability of the procedure, particularly with extended templates and saturation techniques, and should be considered in all patients. For cases such as individuals with anal strictures, those who do not readily tolerate biopsy under local anesthesia, or patients who have been inadequately blocked with a periprostatic injection, deep sedation or general anesthesia may be advantageous.

**NCCN Recommendations**

**General Considerations**

The decision to participate in an early detection program for prostate cancer is complex for both the patient and physician. Important factors must be assessed when considering early detection of prostate cancer, including patient age, life expectancy, family history, African ancestry, presence of inherited mutations, and previous early detection test results (see Screening in High-Risk Populations, above). Most importantly, the patient and physician need to understand the risks and benefits associated with the early detection and treatment of prostate cancer.
Several general principles for early detection should be clearly understood before using the NCCN Guidelines:

- No portion of these early detection guidelines is designed to replace an accurate history and complete physical examination conducted by a physician.

- The general health, medical comorbidities, life expectancy, and preferences of the patient are paramount when recommending or designing an early detection program.

- Prostate cancer risk factors, such as family history, presence of inherited mutations, and African ancestry, should be considered before decisions are made concerning the initiation of an early detection program (see Screening in High-Risk Populations, above).

- Prostate cancer in its early stages has no identifiable symptoms. In advanced disease, symptoms may include urinary obstruction, prostatic bleeding, hematospermia, and bone pain. Although most individuals wishing to take part in early detection programs have no symptoms of prostate cancer, they may have mild to severe symptoms of lower urinary tract disease because of benign prostatic enlargement. Care should be taken to educate patients about the distinction between these two diseases when discussing the risks and benefits associated with early detection.

- A patient’s history of prior testing, including DRE, PSA, PSA derivatives, and prostate biopsy, should be assessed when considering early detection.

- A thorough discussion on the pros and cons of testing must be carried out between the physician and the potential participant as outlined in the algorithm. Patients should be informed that the purpose of early detection is to find aggressive cancers, that early detection often detects low-risk cancers, and that such low-risk cancers may not need treatment but can be managed by active surveillance. Decision aids are available.353-355

- The panel uniformly feels that these guidelines need to be linked to the NCCN Guidelines for Prostate Cancer (available at www.NCCN.org).

- The panel recommends that baseline PSA testing should be offered to healthy, well-informed, average-risk individuals aged 45 to 75 years based on the results of RCTs. Baseline testing may be complemented by DRE. An elevated PSA should be confirmed by repeat testing.

- The panel recommends that baseline PSA testing for healthy, well-informed individuals with African ancestry, germline mutations that increase the risk for prostate cancer, and/or a suspicious family history should be offered at ages 40 to 75 years.

- The panel recommends that frequency of testing be 2 to 4 years for those under age 75 years with serum PSA values below 1 ng/mL. For those with PSA of 1 to 3 ng/mL, testing should occur at 1- to 2-year intervals.

- The panel recommends that multiparametric MRI be performed before biopsy if available. Consideration may be given to biomarkers that improve biopsy specificity such as %f PSA, 4Kscore, SelectMDx, ExoDx Prostate, and PHI before biopsy in those with serum PSA levels of >3 ng/mL who desire more specificity. PHI, %f PSA, 4Kscore, ConfirmMDx, and PCA3 are
also options in individuals thought to be higher risk despite a negative prostate biopsy.

• The panel recommends that biopsy should be considered in those under age 75 years with a repeat serum PSA >3.0 ng/mL. However, the majority of panel members agree that a decision to perform a biopsy should not be based on a PSA cut-point alone, but should incorporate other important clinical variables including age, family history, PSA kinetics, ancestry, health status, and patient preference, as well as results of multiparametric MRI and/or biomarker tests.

• The panel recommends consideration of MRI targeting as an addition to TRUS- or transperineal-guided biopsy in those centers with MRI availability.

• The panel recommends that PSA testing be cautiously considered only in very healthy patients older than 75 years (category 2B) and that indication for biopsy be carefully evaluated. Panel members uniformly discourage PSA testing in individuals unlikely to benefit from prostate cancer diagnosis based on age and/or comorbidity.

Interpretation of Biopsy Results

Cancer
Patients diagnosed with prostate cancer by biopsy should be managed according to the NCCN Guidelines for Prostate Cancer (available at www.NCCN.org). Among patients diagnosed with cancer on prostate biopsy, the panel does not recommend routine repeat biopsy, except in special circumstances, such as 1) there is suspicion that the patient harbors more aggressive cancer than was evident on the initial biopsy; and 2) the patient is otherwise a candidate for active surveillance as outlined in the treatment guidelines.

Intraductal Carcinoma without Invasive Cancer
Intraductal carcinoma (IDC) represents an independent adverse pathologic factor in both radical prostatectomy and needle biopsy specimens that may influence response to current therapeutic regimens for advanced stage prostate cancer. In radical prostatectomy, IDC correlates with other adverse pathologic features in the associated invasive prostate cancer, including higher Gleason score, larger tumor volume, and greater probability of extraprostatic extension, seminal vesicle invasion, and pelvic lymph node metastasis; it also independently predicts biochemical recurrence, progression-free survival, and cancer-specific mortality after radical prostatectomy.356-364

In biopsy specimens, IDC is typically seen with high-grade, high-volume prostate cancer and is associated with adverse findings in radical prostatectomy and poor outcomes. IDC diagnosed in prostate biopsies provided an independent prognostication of early biochemical recurrence, cancer-specific survival, survival in patients with distant metastasis at presentation, and metastatic failure after radiation therapy in intermediate- and high-risk prostate carcinoma.365-367 IDC may be resistant to current therapeutic regimens for aggressive prostate cancer and may require a multimodal approach and novel therapy.368

IDC’s presence in biopsy material strongly suggests the presence of high-grade cancer. Therefore, proceeding directly to definitive therapy should be considered when IDC is seen on biopsy in the absence of invasive carcinoma (see the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org). Otherwise, careful evaluation is indicated, with strong consideration of a repeat biopsy using MRI targeting to look for invasive cancer.

Atypical Intraductal Proliferation without Invasive Cancer
Intraductal proliferations may show a greater degree of architectural complexity and/or cytologic atypia than typical high-grade prostatic
intraepithelial neoplasia (HGPIN; see below), yet fall short of the strict diagnostic threshold for IDC. The preferred terminology for these lesions is “atypical intraductal proliferation (AIP).”369-371 When diagnosed on needle biopsy, AIP is potentially considered a marker of unsampled cancer, and it is associated with a 50% increased risk of invasive carcinoma and/or IDC on repeat biopsy.371,372 One study found that prostate cancer associated with AIP had worse pathologic features than prostate cancer associated with HGPIN.361 Another study found that AIP-associated prostate carcinoma had similar clinicopathologic features to IDC-associated carcinoma.370

When AIP is seen on biopsy in the absence of invasive carcinoma, repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma is recommended.

**High-Grade Prostatic Intraepithelial Neoplasia**

Approximately 10% of patients undergoing biopsy will be found to have HGPIN.373 Cytologically, the nuclear features of HGPIN resemble that of malignant tumors; however, the presence of a basal layer on the acini distinguishes this entity from cancer.

Extended biopsy schemes have resulted in a dramatic decline in the prevalence of cancer detected from a repeat biopsy in patients with HGPIN detected from the initial biopsy. While reports in the sextant biopsy era demonstrated cancer rates of approximately 50%, contemporary series using extended biopsy schemes report rates of approximately 10% to 20% and occasionally higher.374-376

Interestingly, the rates of cancer with repeat biopsy in such patients seem to differ slightly from those who undergo repeat biopsy based on other risk factors, such as age, family history, and PSA. In addition, most detected cancers are low grade.377

Patients with HGPIN should be followed with PSA and DRE at 6- to 24-month intervals and should consider biomarker testing and/or multiparametric MRI. Repeat biopsy with refined biopsy techniques should be performed based on risk. The rationale for considering repeat biopsy in this population is that 1) approximately 15% of the cancers on repeat biopsy are higher grade where treatment may be beneficial; and 2) knowledge of Grade Group 1 cancer may benefit some, especially younger individuals for whom active surveillance may show grade progression over time.

**Atypia, Suspicious for Cancer**

Distinct from HGPIN in which a basal cell layer is present, atypia is characterized by small single-cell layer acini and includes atypical small acinar proliferation (ASAP). Unlike HGPIN, which is a distinct pathologic diagnosis, atypia represents one of two possibilities: 1) normal prostate tissue distorted by artifact; or 2) prostate cancer that does not meet the histologic criteria for a diagnosis of prostate cancer. Because so few glands are present on the biopsy specimen, an unequivocal diagnosis of cancer cannot be established.

Even in the era of extended biopsy schemes, the prevalence of cancer detected from a repeat biopsy in patients with atypia detected from the initial biopsy is quite high: 50% or more, with the most likely area of cancer detection residing in the prostate area demonstrating atypia from the initial biopsy.378,379

Therefore, the panel recommends that, as for patients with HGPIN, follow-up with PSA and DRE at 6- to 24-month intervals is appropriate. The use of biomarker tests that improve the specificity of screening (see Biomarker Testing: PSA Derivatives and Other Tests, above) and/or multiparametric MRI can also be considered in these patients, although it is not known whether these patients receive as much (or more) benefit from these
approaches as patients with a completely negative biopsy. Repeat biopsy with refined biopsy techniques should be performed based on risk.

**Benign Results**

If a biopsy returns as negative for cancer, the panel recommends repeat PSA and DRE at 6- to 24-month intervals with consideration of repeat biopsy based on results. The 20-year cumulative risk of prostate cancer-specific mortality in patients with initial benign biopsy results is low and increases with PSA levels (0.7% for PSA ≤10 ng/mL; 3.6% for PSA >10 to ≤20 ng/mL; and 17.6% for PSA >20 ng/mL). Biomarker tests that improve the specificity of screening (see Biomarker Testing: PSA Derivatives and Other Tests, above) can be considered in patients thought to be at higher risk despite a negative biopsy to inform the decision about performing a repeat biopsy. As discussed in detail above, multiparametric MRI and targeted biopsies or other refined biopsy techniques may also be considered in the evaluation of such patients.

**Summary**

Since the early 1990s, many variants of the tPSA assay have been introduced in attempts to increase the sensitivity of early detection programs or cancer detection while maintaining specificity (elimination of unnecessary biopsies). These NCCN Guidelines recommend a method by which individuals and their physicians can use these new techniques rationally for the early detection of prostate cancer. These guidelines are not designed to provide an argument for the use of population early detection programs for prostate cancer. Rather, they are meant to provide a vehicle by which early detection efforts can be practiced in an evidence-based, systematic fashion in patients who choose to participate in such programs. Whether to treat a patient upon diagnosis is beyond the scope of these guidelines (see the NCCN Guidelines for Prostate Cancer at [www.NCCN.org](http://www.NCCN.org)).

These NCCN Guidelines for Prostate Cancer Early Detection will incorporate recently validated findings if and when they occur. The panel will re-examine the clinical utility of new modalities annually, and the guidelines will be modified accordingly. In addition, future iterations of these guidelines may incorporate new serum markers currently undergoing clinical investigation.

The goal of NCCN and this Guidelines Panel in updating these algorithms is to assist patients and clinicians in choosing a program of early detection for prostate cancer and in making decisions regarding the need for prostate biopsy. Any clinician who uses these guidelines is expected to exercise independent medical judgment in the context of the individual clinical circumstances to determine the patient's need for prostate biopsy. These guidelines will continue to evolve as the field of prostate cancer advances.
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