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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer Early Detection

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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 2.2018 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 1.2018 include:

Discussion
- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2018 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 2.2017 include:

PROSD-2
- Baseline evaluation, modified last bullet: "Family or personal history of *high-risk germline mutations* ~~BRCA 1/2~~."
- Modified last sentence in footnote "c": "If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. *BRCA1/2* pathogenic mutation carriers are associated with an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality.Information regarding ~~BRCA 1/2 gene status~~ *germline mutations* should be used as part of the discussion about prostate cancer screening."
- Added a branch for "Not screened."
- Modified footnote "e": "Testing above the age of 75 years of age should be done ~~with caution and~~ only in very healthy men with little or no comorbidity *to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread screening in this population would substantially increase rates of over-detection and is not recommended*. ~~as a large proportion may harbor cancer that would be unlikely to affect their life expectancy, and screening in this population would substantially increase rates of over-detection. However, a clinically significant small number of men in this age group may present with high-risk cancers that pose a significant risk if left undetected until signs or symptoms develop. Very few men above the age of 75 years benefit from PSA testing.~~
- Modified footnote "f": The ~~reported~~ median PSA values for men aged 40–49 y range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. ~~Therefore, the PSA value of 1.0 ng/mL selects for the upper range of PSA values~~. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and ~~for the~~ aggressive *prostate cancer.* ~~form of the disease~~. The higher above the median, the greater the risk.
- Modified footnote "g": "Men age ≥60 years with serum PSA <1.0 ng/mL have a very low risk of metastases or death due to prostate cancer. ~~and may not benefit from further testing.~~ A PSA cut point of 3.0 ng/mL at age 75 years also carries a low risk of poor outcome."

PROSD-3
- Changed ~~"Consider percent free PSA, 4Kscore, or PHI"~~ to *"Consider biomarkers that improve the specificity of screening*"

PROSD-4
- Atypia, suspicious for cancer and Multifocal high-grade PIN (>2 sites):
  - Modified first bullet "Consider ~~serum or urine tests~~ *biomarkers that improve the specificity of screening* and/or multiparametric MRI."
- Benign and focal high-grade PIN:
  - Modified bullet "Consider ~~percent free PSA, 4Kscore, PHI, PCA3, or ConfirmMDx~~ *biomarkers that improve the specificity of screening* and/or multiparametric MRI and/or refined prostate biopsy techniques
- Footnote "i" is new to the page. "Biomarkers that improve the specificity of detection are not, as yet, recommended as firstline screening tests. 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 the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy. The predictive value of the serum biomarkers discussed above has not been correlated with that of MRI. Therefore, it is not known how such tests could be applied in optimal combination.

INTRODUCTION

The panel recognizes that prostate cancer represents a true spectrum of disease and that not all men 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 (over-treatment) 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 Prostate Cancer Early Detection Guidelines 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 and, specifically, early detection strategies that do not recognize the importance of refined and selective treatment may result in harm.

The guidelines are specifically for men 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 men currently being diagnosed with prostate cancer who can, and should, be monitored for their disease 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.

See Baseline Evaluation (PROSD-2)

Note: All recommendations are category 2A unless otherwise indicated.
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BASELINE EVALUATION

- History and physical (H&P) including:
  - Family cancer history
  - Medications[a]
  - History of prostate disease and screening, including prior PSA and/or isoforms, exams, and biopsies
  - Race[b]
  - Family or personal history of high-risk germline mutations[c]

→

RISK ASSESSMENT

Start risk and benefit discussion about offering prostate screening:
- Baseline prostate-specific antigen (PSA)[d]
- Strongly consider baseline digital rectal examination (DRE)[d]

EARLY DETECTION EVALUATION

Age 45–75 y
- PSA <1 ng/mL, DRE normal (if done) → Repeat testing at 2–4 year intervals[g]
- PSA 1–3 ng/mL,[f] DRE normal (if done) → Repeat testing at 1–2 year intervals
- PSA >3 ng/mL[f] or very suspicous DRE → See Indications for Biopsy (PROSD-3)

Age >75 y, in select patients (category 2B)[e]
- PSA <4 ng/mL, DRE normal (if done), and no other indications for biopsy → Repeat testing in select patients at 1–4 year intervals
- PSA ≥4 ng/mL or very suspicous DRE → See Indications for Biopsy (PROSD-3)
- Not screened[e]

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

[b]African-American men have a higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to Caucasian-American men. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Consequently, it is reasonable for African-American men to begin discussing PSA screening with their providers several years earlier than Caucasian-American men and to consider screening at annual intervals rather than every other year. Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. Cancer 2017;123:2312-2319.

[c]If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. *BRCA1/2* pathogenic mutation carriers are associated with an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. Information regarding germline mutations should be used as part of the discussion about prostate cancer screening.

[d]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, but should be performed in those with an elevated serum PSA. DRE may be considered as a baseline test in all patients as it may identify high-grade cancers associated with "normal" serum PSA values. Consider referral for biopsy if DRE is very suspicious. Prognostic significance of digital rectal examination and prostate specific antigen in the prostate, lung, colorectal and ovarian (PLCO) cancer screening arm. J Urol 2017;197:363-368.

[e]Testing after 75 years of age should be done only in very healthy men with little or no comorbidity to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread screening in this population would substantially increase rates of over-detection and is not recommended.

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

[g]Men aged ≥60 years with serum PSA <1.0 ng/mL have a very low risk of metastases or death due to prostate cancer. A PSA cut point of 3.0 ng/mL at age 75 years also carries a low risk of poor outcome.

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INDICATIONS FOR BIOPSY[h]

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

→

MANAGEMENT

- Consider biomarkers that improve the specificity of screening[i]
- Consider multiparametric MRI[j]

→

Transrectal ultrasound (TRUS)-guided biopsy[k] → See Management of Biopsy Results (PROSD-4)

or

Follow-up in 6–12 mo with PSA/DRE[i,l]

TRUS-GUIDED BIOPSY
Initial and Repeat
Extended-pattern biopsy (12 cores)
- Number of cores:
  - Sextant (6),
  - Lateral peripheral zone (6), and
  - Lesion-directed at palpable nodule or suspicious image
- Anteriorly directed biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
- Multiparametric MRI followed by lesion targeting may maximize the detection of higher-risk disease and limit the detection of lower-risk disease.[j]
- Local anesthesia can decrease pain/discomfort associated with prostate biopsy and should be offered to all patients.

[h]The level of PSA correlates with the risk of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) demonstrated that 15% of men 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 men with serum PSA between 4 to 10 ng/mL will be found to have cancer. Total PSA levels >10 ng/mL confer a greater than 67% likelihood of prostate cancer.

[i]Biomarkers that improve the specificity of detection are not, as yet, recommended as firstline screening tests. 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 the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy. The predictive value of the serum biomarkers discussed above has not been correlated with that of MRI. Therefore, it is not known how such tests could be applied in optimal combination.

[j]Emerging data suggest that, in men undergoing initial biopsy, targeting using MRI/ultrasound fusion may significantly increase the detection of clinically significant, higher-risk (Gleason grade ≥ 4+3=7) disease while lowering the detection of lower-risk (Gleason sum 6 or lower-volume Gleason grade 3+4=7) disease. Siddiqui M, Rais-Bahrami S, Turkbey B, et al. Comparison of MRI/ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-7. Ahmed H, Bosaily A, Brown L, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-822.

[k]For patients with abnormal DRE, biopsy or additional testing should be considered based on concern for cancer.

[l]Patients with a persistent and significant increase in PSA should be encouraged to undergo TRUS-guided biopsy.

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MANAGEMENT OF BIOPSY RESULTS

Cancer → See NCCN Guidelines for Prostate Cancer

Atypia, suspicious for cancer →
High-grade prostatic intraepithelial neoplasia (PIN) → **Multifocal (>2 sites)** →

Follow-up:
- **Consider biomarkers that improve the specificity of screening[i] and/or multiparametric MRI**
- **Consider repeated biopsy with relative increased sampling of the atypical site**

High-grade prostatic intraepithelial neoplasia (PIN) → **Focal[m,n,o]** →
Benign[m,n,o] →

Follow-up:
- **PSA and DRE at 6- to 24-month intervals**
  and
- **Consider biomarkers that improve the specificity of screening[i] and/or multiparametric MRI and/or refined prostate biopsy techniques[o]**

Repeat prostate biopsy, based on risk

[i] Biomarkers that improve the specificity of detection are not, as yet, recommended as firstline screening tests. 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 the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy. The predictive value of the serum biomarkers discussed above has not been correlated with that of MRI. Therefore, it is not known how such tests could be applied in optimal combination.

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

[n] PSA testing may be discontinued at certain ages and PSA cutpoints, as noted in the discussion section.

[o] Emerging evidence suggests that use of multiparametric MRI and/or use of refined prostate biopsy techniques (image guidance using MRI/ultrasound fusion, transperineal, or saturation prostate biopsies) may be of value. These techniques may help identify regions of cancer missed on prior prostate biopsies and should be considered in selected cases after at least 1 negative prostate biopsy. Multiparametric MRI followed by lesion targeting may maximize the detection of higher-risk disease and limit the detection of lower risk disease.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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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 a screening 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 men 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 screening only in healthy men. 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 men. In 2018, it is estimated that 164,690 men will be diagnosed with prostate cancer and 29,430 will die of this disease.[1] During the same period, nearly 20 million men in the United States will be confronted with important decisions regarding early detection for prostate cancer. Men born in the United States have about 1 chance in 7 of eventually being diagnosed with this malignancy and about 1 chance in 39 of eventually dying of it.[2] By 2015, death rates for prostate cancer in the United States had fallen 47% from peak rates, largely due to early detection and improved treatment.[3]

The panel supports the continued use of prostate-specific antigen (PSA) testing for the early detection of prostate cancer in informed, healthy men 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 men 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 men 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 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 and articles from additional sources (eg, e-publications ahead of print, meeting abstracts) deemed as relevant to these Guidelines and discussed by the panel 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 on the NCCN website (www.NCCN.org).

Types of Early Detection Testing

PSA Testing

PSA is a glycoprotein secreted by prostatic epithelial cells, and its protease activity lyses 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. One study showed that approximately 25% of men 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 men with elevated PSA levels do not have prostate cancer. In fact, only about 25% of men with PSA in the 4 to 10 ng/mL range have a subsequent positive biopsy.[6] Still, men with low PSA values have a significant chance of having prostate cancer. Using data from 18,882 men in the Prostate Cancer Prevention Trial (PCPT), Thompson et al[7] 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%.

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.

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.[8] 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.[9] 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. The PCPT demonstrated that 15% of men 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).[10] Approximately 30% to 35% of men with serum PSAs in the 4 to 10 ng/mL range will be found to have cancer. Total PSA (tPSA) levels >10 ng/mL confer a greater than 67% likelihood of biopsy-detectable prostate cancer.[11]

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 men with an elevated PSA.[12]

The 5α-reductase inhibitors (5-ARI) 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.[13] However, this effect is tremendously variable. For example, one study showed that after 12 months of treatment, only 35% of men demonstrated the expected 40% to 60% decrease in PSA, while another 30% had greater than a 60% decrease.[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,[15,16] but reflex ranges for PSA among patients on 5-ARIs have not been established. The PCPT of 18,882 men demonstrated that finasteride reduced the incidence of prostate cancer by 25% compared to placebo. This reduction was almost exclusively for low-grade (Gleason sum 6) tumors; an increased proportion of aggressive (Gleason sum ≥7) tumors was seen.[17] However, after 18 years of follow-up, there was no significant group difference in overall survival or survival after the diagnosis of prostate cancer in those on finasteride compared to the control group.[18]

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.[15] Similar to the PCPT trial, the difference in the number of high-grade cancers detected did not result in a mortality difference.[19]

A report on the Combination of Avodart (dutasteride) and Tamsulosin (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.[16] Unlike the PCPT and REDUCE studies, diagnosis of high-grade (Gleason sum ≥7) tumors was not increased. Overall, these studies suggest that PSA testing may have enhanced specificity for men receiving finasteride or dutasteride. Whether or not men should consider taking these agents for chemoprevention is beyond the scope of this guideline.

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,[20] recent ketoconazole use should also be noted in the history.

A health survey on 12,457 men visiting a prostate cancer screening clinic showed that over 20% of the men took herbal supplements, while only 10% took prescription medication (such as finasteride) for lower urinary tract symptoms.[21] 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.[22-27] 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.[28,29] This trend has likely, but not positively, contributed to a substantial reduction in prostate cancer mortality.[30,31]

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 overdetection, which is the identification of indolent disease, disease that would not be a problem for the patient if undetected or untreated. These arguments hold that overdetection may lead to overtreatment, which is aggressive treatment in men 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.[32] 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.[33] After this recommendation, prostate cancer screening decreased, as did biopsy rates, diagnoses of localized prostate cancers, and radical prostatectomy rates.[34-43] The effect of the 2012 USPSTF recommendations on the rate of diagnoses of metastatic prostate cancer is, however, unclear, with some studies showing an increase and others showing none.[39,40,44,45]

The USPSTF released updated draft recommendations in 2017 and is currently working on a final recommendation statement.[46] The draft recommendations are: 1) against prostate cancer screening in men aged 70 years and older; and 2) for individualized, informed decision-making regarding prostate cancer screening in men aged 55 to 69 years. For men in this younger age group, clinicians should inform them regarding the potential harms and benefits of PSA-based screening. The draft USPSTF statement does not provide guidance for men 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.[47,48] Currently, 81% of prostate cancers are pathologically organ-confined at time of diagnosis.[49]

Recent screening trials have either used DRE in conjunction with PSA for screening[50] or as an ancillary test for patients who are found to have an elevated PSA.[51,52] To elucidate the specific role of DRE in screening for prostate cancer, Gosselaar and colleagues[53] showed that among those with a serum PSA >3 ng/mL, those with a positive DRE were more likely to have prostate cancer. Furthermore, among 5519 men in the control arm of the PCPT, Thompson and colleagues[54] 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 Gleason score ≥7 prostate cancer in men with PSA ≥3 ng/mL (23.0% risk at 10 years vs. 13.7% risk at 10 years in men with non-suspicious DRE), but not in men with PSA <2 ng/mL (1.5% vs. 0.7%).[55] Ten-year risk in men with PSA in the 2 to 3 ng/mL range were 6.5% in men with suspicious DRE compared with 3.5% in men with non-suspicious DRE.

In a secondary analysis of the PLCO trial, in which participants were screened with PSA and DRE, only 15.4% of men with a suspicious DRE had an elevated PSA.[56] On multivariate analysis, 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 men directly compared the efficacy of PSA and DRE in the early detection of prostate cancer.[57] 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 DRE in men with normal PSA is poor (about 4%–21%).[57-59] 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 men with low PSA values. In fact, in an analysis of 166,104 men 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), Gleason score 8–10 prostate cancer.[60]

Overall, the panel believes that the value of DRE as a stand-alone test for prostate detection is limited, even though 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 should be strongly considered with serum PSA in asymptomatic men who had a risk/benefit discussion and decided to pursue screening for prostate cancer. Those with a very suspicious DRE should be considered for biopsy referral regardless of PSA results, because it may identify high-grade cancers in such situations. Furthermore, the panel believes that DRE should be performed in all men 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, 2 studies are most relevant due to their topicality and randomized design.

ERSPC Trial

The ERSPC involved about 182,000 men between the ages of 50 and 74 years in 7 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.[52,61] The predefined core group included 162,388 men 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 men would need to be screened and 37 additional men would need to be treated over 11 years to prevent one prostate cancer death. Modeling the ERSPC data, however, Heijnsdijk and colleagues[62] 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.[63] 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 men 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 men were diagnosed with metastatic disease in the screening arm (incidence rate ratio, 0.60; 95% CI, 0.52–0.70).[64]

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%.[65] This same group found that if one controlled for noncompliance and nonattendance, the risk of death due to prostate cancer can be reduced by up to 51%.[66]

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.[67]

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.[51] Twenty thousand men 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 men who have not reached the upper age limit invited for PSA testing. In men 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 men 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 compared with the control group. Overall, 293 men 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 recently reported, with 1396 cases of prostate cancer in the screening arm and 962 cases in the control arm.[68] 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, men 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.[69]

PLCO Trial

The PLCO study randomized 76,685 men 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.[70] 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.[71]

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 men in the usual care arm were screened at least once). The high contamination rates have been confirmed by others.[72,73] 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.[74]

A recent 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).[75]

In a subset analysis of PLCO reported by Crawford and colleagues,[76] a 44% decrease in the risk of prostate cancer-specific death was observed in men 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 men with one or more significant comorbidities. These results suggest that screening is more useful among men in good health due to the lack of competing cause for mortality. However, others suggest that such analysis is prone to major methodologic errors.[77]

CAP Trial

The results of the Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP) were recently reported.[78] 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 has 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 a 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 men with high-risk factors. For instance, <5% of PLCO participants were of African-American descent and only 7% reported a family history of prostate cancer.[50] Therefore, it is not known whether men at higher risk may benefit more from screening than those at lower risk. Second, many men 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 above 60), 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 men with prostate cancer identified by screening.[62]

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 men aged 55 to 69 years. The ERSPC and Göteborg trials reported decreased disease-specific mortality in men aged 55 to 69 and 50 to 64 years, respectively. These results support baseline PSA testing in men aged 50 to 55 years with the strongest evidence supporting testing at age 55. Recent analyses of PSA testing in Swedish men aged 50 to 54 years support screening in this younger cohort.[79]

As even younger men 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 men in their 40s and early 50s may have value for future risk stratification, although some would describe the value as marginal.[80] A study by Lilja and colleagues[81] assessed blood collected from 21,277 men 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 risks of unnecessary biopsies and prostate cancer overdetection are likely increased with earlier initiation of screening.[82]

Another report clarified associations of age with the long-term risks of metastases.[83] In this study, the risk of prostate cancer death was strongly correlated with baseline PSA in men aged 45 to 49 years and 51 to 55 years; 44% of the deaths in the analytic cohort occurred in men in the highest tenth of the distribution of PSA, suggesting that there may be a strong rationale for baseline testing in men younger than age 55 years.

In a nested case-control study of men 40 to 59 years of age in the Physicians' Health Study, baseline PSA strongly predicted lethal prostate cancer later in life.[84] For example, men aged 55 to 59 years with PSA levels above the 90th percentile had an odds ratio of 6.9 (95% CI, 2.5–19.1) for lethal prostate cancer compared with men whose PSA levels were at or below the median.

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 men thought to be at higher risk due to family history or race, 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 men who have a PSA value ≥1.0 ng/mL and at 2- to 4-year intervals for men with PSA <1 ng/mL (also see *Frequency of Testing,* below). This value is above the 75th percentile for younger men (<50 years).[85] 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.[86,87]

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 men aged 55 to 64 years.[88] The Göteborg arm randomized 4202 men to screening every 2 years, while the Rotterdam arm randomized 13,301 men 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; Gleason >8 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 micro-simulation models of prostate cancer incidence and mortality predicted that a strategy that utilizes biennial intervals in men with average PSA levels and longer screening intervals (every 5 years) for men 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.[89] 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 men with a very low PSA could safely extend the testing interval. In the Rotterdam section of the ERSPC trial, men with a PSA <1 ng/mL had a very low risk for cancer at 4 and 8 years (0.23% and 0.49%).[90] Other studies have shown that PSA values at younger ages strongly predict the development of or death from prostate cancer.[87,91] For example, in a Swedish case-control study of 1167 men, 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.[91]

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 men aged 45 to 75 years. The panel notes that a younger man on the higher end of PSA (eg, a 45-year-old man with PSA 0.9 ng/mL) might be screened in 2 years, whereas an older man 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 men with normal PSA levels.

Panelists uniformly agreed that PSA testing should only be offered to men with a 10 or more year life expectancy. However, panelists did not agree as to when to discontinue routine testing in asymptomatic older men. Furthermore, estimates of life expectancy can be refined using several resources such as life insurance tables.[92-94] Physicians may not be accurate at estimating life expectancy and many tend to overvalue age and undervalue comorbidity.[95,96]

Since the previously cited RCTs (ERSPC, PLCO, and Göteborg) observed benefits to testing only in men 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 men who underwent radical prostatectomy found that men older than 70 years were more likely to have higher grade and stage of disease and worse survival compared to their younger counterparts.[97] Others have published similar findings.[98]

To assess the appropriate ages for discontinuing screening, the previously cited micro-simulation model[89] 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 men 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 overdetection, while also recognizing the increased prevalence of higher-risk cases in this age that could benefit from earlier detection.

The micro-simulation model also assessed a strategy of screening men 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[91] 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 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 men in the Baltimore Longitudinal Study of Aging (BLSA), no men aged 75 to 80 years with a PSA <3.0 ng/mL died of prostate cancer.[99] Moreover, the time to death or diagnosis of aggressive prostate cancer was longer in men with a PSA <3.0 ng/mL versus those with a PSA >3.0 ng/mL, suggesting that men 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. At this time, the panel supports screening in men until age 75. Continuing screening beyond this age should be only with caution in very healthy patients with little to no comorbidity (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 screening in this population would substantially increase rates of overdetection and is not recommended. Older men who do chose 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 PSA ≥4 ng/mL or a very suspicious DRE should be considered for biopsy as indicated in the guidelines.

Screening in High-Risk Populations

African-American men and men with a first-degree relative with prostate cancer (especially cancer found at a younger age) have a higher risk of developing prostate cancer.[100-107] In fact, 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.[103,104] A population-based study in Sweden found that the risk for the development of prostate cancer increased with the number of affected relatives.[108] Data, however, suggest that prostate cancer in men 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.[106,109,110] It is also important to note that, because men with a family history of prostate cancer are more likely to undergo screening and biopsy than men without a family history, the role of family history as a risk factor for prostate cancer may be overestimated.[111] Welch and Brawley refer to this phenomenon as "self-fulfilling risk factors" in cancers that are "scrutiny-dependent."[112]

African-American men have a 64% higher incidence of prostate cancer and a 2.3-fold increase in prostate cancer mortality compared with Caucasian men.[100,113] Furthermore, autopsy data indicate that prostate cancer may undergo transformation to aggressive disease earlier in African-American men than in Caucasian men.[113] In addition, data suggest that African-American men have an earlier onset of prostate cancer. An analysis of SEER data from 2010 found that non-Hispanic African-American men are diagnosed with prostate cancer an adjusted average of 1.2 years earlier than non-Hispanic white men;[114] whereas an older SEER analysis found that African-American men were diagnosed at an average of 3 years younger than Caucasian men.[115] A retrospective, population-based cohort study in the United Kingdom found that men of African descent were diagnosed an adjusted average of 5.1 years earlier than Caucasian men.[116] Another study estimated that African-American men have an almost 2-fold higher risk of being diagnosed with prostate cancer before the age of 45 than Caucasian men.[115] In addition, a recent study of 41,250 men in the Veterans Affairs (VA) Health Care System database found that the optimal PSA threshold for predicting the diagnosis of prostate cancer within 4 years was lower in African-American men than in Caucasian men (1.9 ng/mL vs. 2.5 ng/mL).[117] Finally, modeling studies indicate that African-American men likely have higher incidence of preclinical disease and an increased risk of metastatic progression than Caucasian-American men.[118]

Factors that contribute to this racial disparity may include differences in genetic risk factors, environmental exposures, and patient and physician behaviors; decreased access to high-quality health care, including cancer early detection and follow-up care; delays in diagnosis; and suboptimal treatment.[119-123]

Prostate cancer screening has been best studied in Caucasian men; 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.[50] In the ERSPC trial, no information on race or family history was reported.[52]

In conclusion, African-American men and men with a family history of prostate cancer represent high-risk groups. However, the panel believes that current data are insufficient to definitively inform the best strategy for prostate cancer screening in these populations, and also notes that a baseline PSA value is a stronger predictive factor than a positive family history or race.[124] Overall, the panel believes that it is reasonable for African-American men and those with a strong family history to begin discussing PSA screening with their providers earlier than those without such risk factors and to consider screening at annual rather than less frequent screening intervals. Recent information suggests that screening high-risk groups, including those of low socioeconomic status, is of benefit.[125,126]

Prostate Cancer Risk in Genetic Syndromes

Recent data indicate that men 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*.[127] Men with these inherited syndromes have an increased risk for prostate cancer. For example, men 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.[128-133] Age of onset and aggressiveness of prostate cancer in these individuals, however, do not generally appear to be different than in sporadic cases.[129,132] Currently, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org) do not list any specific prostate cancer screening recommendations for men with Lynch syndrome.

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.[134,135] *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.[136,137] These mutations have been associated with an increased risk for prostate cancer in numerous reports.[138-147] 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.[139,141,142,147-149] Furthermore, prostate cancer in men 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.[150-155] Among lethal prostate cancer cases, 60% of mutation carriers of *BRCA1/2* and *ATM* report a negative family history.[152]

Results from the first round of screening of the IMPACT study, which enrolled men aged 40 to 69 years with germline *BRCA1/2* mutations and a control group of men with wild-type *BRCA1/2* who are related to mutation carriers, were recently reported.[156] Whereas it was evident that there was no difference between carriers and controls in the rate of prostate cancer detection or the PPV of biopsy for detecting cancer in men with PSA >3.0 ng/mL, a significant difference was seen in the PPV of biopsy for detecting intermediate/high-grade cancer in *BRCA2* carriers with PSA >3.0 ng/mL (2.4% vs. 0.7%; *P* = .04). Future rounds of screening in this trial may help inform the best strategy for screening in this high-risk population.

The V.1.2018 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at www.NCCN.org) recommend that men with *BRCA2* mutations start prostate cancer screening at age 45 and that men with *BRCA1* mutations consider the same. At this time, the NCCN Prostate Cancer Early Detection Panel believes that data supporting a change in the PSA screening and biopsy recommendations for men with germline *BRCA1/2* mutations relative to men without mutations are insufficient for them to have separate screening recommendations. 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 and Ovarian 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 screening; patients may not be aware of the increased risk for prostate cancer associated with such mutations.

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. 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, race, 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 men with low PSA. The PPV of DRE in men with low PSA is poor (see *DRE*, above).[59,157] However, a very suspicious DRE, independent of PSA, could be an indication of high-grade cancer in men with normal PSA values, and therefore biopsy can be considered. Clinical judgment should be used.

Pre-Biopsy Workup

The panel recommends that any man 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. A DRE in this setting of elevated PSA has a high predictive value,[53] and the panel strongly recommends biopsy in these men. 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 with that of multiparametric MRI. Therefore, it is not known how such tests could be applied in optimal combination.

Men 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.[54,158-163] These online tools combine clinical variables—including but not limited to age, family history, race, 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.[164] 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.

Imaging

The Prostate Imaging Reporting and Data System (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.[165] In addition, the European Society of Urogenital Radiology established guidelines for optimal multiparametric MRI of the prostate, including for detection and targeted biopsies.[166] Overall, the panel emphasizes the need for high-quality MRI and for radiologic expertise for optimal reading of scans.

Novel Imaging Techniques

There is considerable interest in the use of novel MRI imaging, most notably multiparametric MRI, to select those who need a prostate biopsy or to guide needle placement during the biopsy.[167-173] The goals of using MRI to inform the decision to perform biopsy include reducing the number of men undergoing biopsy, reducing the detection of indolent disease (and thus the risks of overdetection and overtreatment), and improving the detection of clinically significant disease through targeted biopsies.

In a prospective study of 223 biopsy-naïve men with elevated PSA, all men had standard TRUS biopsies in addition to multiparametric MRI.[169] Participants with suspicious or equivocal lesions (PI-RADS 3-5) then underwent MRI-guided biopsy. TRUS biopsies detected 126 of 142 cancer cases (88.7%), including 47 cases classified as low risk. The MRI-guided biopsies identified an additional 16 cases of intermediate/high-risk prostate cancer and led to the reclassification of 13 cases from low risk to intermediate/high risk. Thus, the addition of multiparametric MRI with targeted biopsies for suspicious or equivocal lesions to standard biopsy allowed the identification of clinically significant disease in an additional 13% of the study population. The authors also determined the effects of using multiparametric MRI to decide whether to biopsy. Not biopsying men with PI-RADS 1/2 would reduce the number of men requiring biopsy by 36%, reduce the identification of low-risk prostate cancer by 87%, and increase the yield of intermediate/high-risk tumors by 18%, but would have missed 15 intermediate/high-risk tumors (6.7% of study population).

A single-center trial randomized 130 biopsy-naïve men to a control group that received TRUS-guided random biopsy alone or to a group that received prebiopsy multiparametric MRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion-targeted biopsy.[171] The primary outcome was not met, with similar rates of detection of prostate cancer (64% vs. 57%; $P = .5$) and of clinically significant cancer (55% vs. 45%; $P = .8$) in the two arms.

In a prospective cohort study of 1003 men with elevated PSA or abnormal DRE and lesions visible on multiparametric MRI undergoing both MRI/ultrasound (US) fusion-targeted and standard biopsy, Siddiqui and colleagues noted that the targeted biopsy strategy was associated with increased detection of high-risk (Gleason sum ≥ 4 + 3) cancer and decreased detection of low-risk (Gleason sum 6 or low-volume 3 + 4 = 7) cancer.[174] Additional clinical trials are underway to assess the value of MRI imaging for diagnosis in the pre-biopsy setting (eg, NCT02131207).

In a multicenter, paired-cohort study, 576 men with elevated PSA <15 ng/mL underwent multiparametric MRI followed by TRUS biopsy and template prostate mapping biopsy.[175] Forty percent were diagnosed with clinically significant prostate cancer, defined as Gleason score ≥4 + 3 or a maximum cancer core length 6 mm or longer by template prostate mapping biopsy. The sensitivity and specificity of multiparametric MRI for the detection of clinically significant prostate cancer were 93% (95% CI, 88%–96%) and 41% (95% CI, 36%–46%), whereas the sensitivity and specificity of TRUS-guided biopsy were 48% (95% CI, 42%–55%) and 96% (95% CI, 94%–98%). Thus, in this study, using a negative multiparametric MRI to avoid biopsy in men with elevated PSA would have allowed 27% of patients to avoid biopsy and would have resulted in a 5% decrease in the diagnosis of clinically insignificant cancers. Clinically significant cancer would have been missed in 17 patients (3%).

Results of a multicenter, randomized, non-inferiority trial that compared the use of MRI before a targeted biopsy to standard ultrasound-guided, 10–12 core biopsy were recently reported.[176] In the MRI group, 28% of men had exams not suggestive of cancer and did not undergo biopsy. Clinically significant cancer was detected in 38% of the MRI group and in 26% of the standard biopsy group. Fewer men in the MRI group received a diagnosis of low-risk disease. Other studies have similarly shown that the use of multiparametric MRI can reduce the number of negative biopsies in either the initial or repeat biopsy settings.[177-181]

At this time, the panel believes that the use of multiparametric MRI can 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 an option.[182]

The panel does not uniformly recommend that MRI-guided targeted biopsies be used in place of or in addition to standard 12-core TRUS biopsies in the initial biopsy setting (see *Targeted Biopsy Techniques for Initial Biopsy,* below), because some significant cancers may sit outside targets identified on MRI. More information is needed in such a setting. However, the panel believes that multiparametric MRI may help identify regions of cancer missed on prior biopsies and should be considered in selected cases of men with at least 1 negative biopsy (also see *Repeat Biopsies*, below).[183]

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 probability of cancer before proceeding to biopsy with its associated risks (see *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 (Gleason ≥7) cancers. These tests may be especially useful in men 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 percent free PSA (%f PSA), Prostate Health Index (PHI), and 4Kscore®, in patients with PSA levels >3 ng/mL who have not yet had a biopsy. %f PSA, PHI, 4Kscore, PCA3, and ConfirmMDx may also be considered for men who have had at least one prior negative biopsy and are thought to be at higher risk. 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.

Head-to-head comparisons have been performed in Europe for some of these tests, used independently or in combinations in the initial or repeat biopsy settings, but sample sizes were small and results varied.[184-195] 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 in the repeat biopsy setting (discussed below).[196] 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. Results of any of these tests, when performed, should be included in discussions between clinician and patient to assist in decisions regarding whether to proceed with biopsy. These and other tests are discussed below.

Age- and Race-Specific PSA Reference Ranges

Age-specific PSA reference ranges were introduced by Oesterling and colleagues[197] as a method to increase cancer detection (ie, increase sensitivity) in younger men by lowering PSA cutoffs for biopsy and to decrease unnecessary biopsies (ie, improve specificity) in older men by increasing PSA cutoffs.[197-199] Several groups have investigated these age-specific ranges with equivocal results. Others have suggested race-specific reference ranges.[200] However, the exact roles of these age- and race-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 3 separate PSA values calculated over at least an 18-month period. Carter and colleagues[201] first showed that PSAV is greater in men eventually diagnosed with prostate cancer than in men not diagnosed with the disease and suggested its use as a screening tool. In a subsequent study of 980 men 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 men 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).[202] 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 men with prostate cancer,[203,204] 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,[205] however, have questioned the role of PSAV in tumor detection among men with low PSA levels. The analysis was performed on 5519 men 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 men recommended for biopsy. However, these findings should be applied only to men similar to those studied in PCPT (≥55 years of age; 96% Caucasian-American; 17% family history of prostate cancer; PSA values ≤3 at enrollment).[54] A recent report suggests that screening strategies that utilized PSAV at low PSA levels were more likely to suffer from overdiagnosis and false-positive tests resulting in more harm relative to incremental lives saved.[89]

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 men with PSA >3.0 ng/mL.[206] However, in a study of men 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.[207]

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 men 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 decision-making process. Other factors such as age, comorbidity, race, 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;[54,203,208] PSAV is not useful in patients with very high (>10 ng/mL) PSA values;[209] PSAV measurements can be confounded by prostatitis, a condition that can cause dramatic and abrupt increases in PSA levels;[210] 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 men, 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 percentage of serum fPSA (%f PSA) is significantly lower in men who have prostate cancer compared with men who do not.

The FDA approved the use of %f PSA for the early detection of prostate cancer in men with a normal 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.[211]

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 men, of whom 313 had prostate cancer, researchers found that cPSA in the range of 80% to 95% sensitivity thresholds increased specificity compared with tPSA.[212] Results were similar for %cPSA and %fPSA.

Therefore, the ratio of cPSA to tPSA should provide information comparable to the fPSA to tPSA ratio.[213] Other studies also demonstrated an enhanced specificity of cPSA within certain tPSA ranges.[214-216] Use of cPSA has been approved as an aid in the detection of prostate cancer in men 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

PSA density (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.[217,218] Thus, PSAD potentially identifies men 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 men from unnecessary biopsies. However, some subsequent studies have reported that the 0.15 cutoff has insufficient sensitivity.[219]

More recent studies have tried to improve upon the performance of PSAD by using cPSA[220] or fPSA[221] in the numerator or correcting the denominator for transition zone volume.[222] 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.[223,224]

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.[225]

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 US. Still, the panel agrees that PSAD has been clinically under-utilized 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.[226-229] For example, in a prospective multicenter clinical study of 466 men with at least 1 prior negative prostate biopsy, a PCA3 score cutoff of 25 showed a sensitivity of 78%, specificity of 57%, negative predictive value (NPV) of 90%, and PPV of 34%.[226] Men 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 men scheduled for a diagnostic prostate biopsy in 11 centers.[230] 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 men with a low PCA3 score would have high-grade prostate cancer that would be missed. In contrast, the risk of high-grade disease in men without prior biopsy with a low PCA3 is 13%. Thus, the panel believes that this test in 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 men with previous negative biopsy in order to avoid repeat biopsy by the Molecular Diagnostic Services Program (MolDX) and is therefore covered by CMS (Centers for Medicare & Medicaid Services) in this setting.

PHI

The PHI is a combination of the tPSA, fPSA, and proPSA tests.[231-233] 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.[234] In addition, the PHI correlated with cancer grade and had an area under the curve (AUC) of 0.72 for discrimination of high-grade (Gleason ≥7) cancer from low-grade cancer or negative biopsy. Another prospective cohort study calculated an AUC of 0.815 for the detection of high-grade (Gleason score ≥7) prostate cancer.[235] 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.[196,236-238]

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 4 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%; $P < 0.0001$).[239] Patients in the study had a 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.

4Kscore

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.[240,241] This test reports the percent likelihood of finding high-grade (Gleason ≥7) 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).[242] 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 men in another prospective study, the AUC was also 0.82 (95% CI, 0.80–0.84).[243] Using a 6% risk of high-grade cancer as a cutoff, 428 of 1000 men 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.[244] 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 prostate cancer with a Gleason score ≥7 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 cut-off 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 men 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 men with negative biopsies who had repeat biopsies within 30 months.[245] The NPV was 90% (95% CI, 87%–93%). In 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 men with negative biopsies who had repeat biopsies within 24 months.[246] 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 men 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.

Additional Biomarker Tests

The list of assays with the potential to permit improved detection of Gleason score ≥7 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 Gleason 6 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 of men is needed before they can be accepted as alternatives to (or perhaps preferable to) other tests, described above.

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.[247] This gene panel proposes to discriminate prostate cancer with a Gleason score of ≥7 from that with a Gleason score of 6 and benign disease at initial biopsy. The population for which use of the assay was intended to be used 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.[248] 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 Gleason score ≥7 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 developed for the first time in 255 patients and then validated in the extended screening group of 519 patients, representing only 48% of the validation cohort after multiple exclusions. The majority of exclusions were for urine volume >49 mL, assay failure, and application outside the intended use population.

Based on reasons discussed above (see *Additional Biomarker Tests*), the panel considers EPI to be investigational at the present time, but will review additional information as it becomes available.

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.[249] Rearrangements of the *ERG* gene are found in approximately half of prostate cancers.[250] The *TMPRSS2:ERG* fusion specifically occurs at high frequency and appears to be an early event in prostate cancer development.[251] The role of PCA3 in prostate cancer is discussed above. Early studies suggested that the combination of these 2 markers improved the prediction of prostate cancer on biopsy.[252]

A MiPS validation study included 1244 men with planned biopsy (80% with no prior prostate biopsy) in a validation cohort.[249] The AUC for the prediction of any cancer was 0.751 for MiPS, compared with 0.585 for PSA alone. For the prediction of Gleason score ≥7 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.[253] In the validation cohort, use of the test improved specificity for the presence of cancer with Gleason score ≥7 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.

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.[254,255] As with other assays, SelectMDx is designed to improve the identification of men 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 2 prospective multicenter studies and was then validated in a separate set of 386 patients from these trials.[256] 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 Gleason score ≥7 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 mpMRI results in 172 patients who had mpMRI because of persistent clinical suspicion of prostate cancer or for local staging after positive biopsy.[257] The AUC of SelectMDx for the prediction of mpMRI outcome was 0.83, whereas the AUC for PSA and PCA2 were 0.66 and 0.65, respectively.

Based on reasons discussed above (see *Additional Biomarker Tests*), the panel considers SelectMDx to be investigational at the present time, but will review additional information as it becomes available.

Biopsy Technique

Initial Biopsy

Systematic prostate biopsy under TRUS guidance is the recommended technique for prostate biopsy. Initially described as a sextant technique sampling both right and left sides from the apex, mid-gland, and base in the mid-parasagittal plane, more recently extended biopsy schemes have demonstrated improved cancer detection rates. Although no one scheme is considered optimal for all prostate shapes and sizes, most emphasize better sampling of the lateral and anterior aspects of the peripheral zone. One commonly used scheme is the 12-core biopsy scheme that includes a standard sextant as well as a lateral sextant scheme (ie, lateral apex, lateral mid-gland, lateral base). This scheme has been validated and results in enhanced cancer detection compared to sextant biopsy schemes.[258,259]

The panel recommends an extended-pattern, at least 12-core biopsy be done (sextant medial and lateral peripheral zone and lesion-directed). 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.

Interest in the use of novel imaging, particularly MRI, to guide needle placement during biopsy (see *Imaging,* above, and *Targeted Biopsy Techniques for Repeat Biopsy*, below) has recently increased.[260] In addition, there is interest in saturation approaches to biopsy (often image-guided) to improve diagnostic accuracy (see *Saturation Biopsy Techniques*, below).[261] Another advanced prostate biopsy technique is transperineal template biopsy, which systematically samples anterior, mid, posterior, and basal zones for approximately 24 to 32 cores.[262]

At present, the panel does not recommend routine use of advanced biopsy techniques or specific imaging other than TRUS for initial biopsy, although they can be considered in the repeat biopsy setting as discussed below.

Targeted Biopsy Techniques for Initial Biopsy

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).[260,263,264] Emerging data suggest that multiparametric MRI followed by lesion targeting may increase the detection of clinically significant, higher-risk (Gleason ≥ 4+3) disease while lowering the detection of lower-risk (Gleason 6 or lower-volume 3+4) disease.

In a prospective study of 223 biopsy-naïve men with elevated PSA, all men had standard TRUS biopsies in addition to multiparametric MRI.[169] Participants with suspicious or equivocal lesions (PI-RADS ≥3) then underwent MRI-guided biopsy. TRUS biopsies detected 126 of 142 cases of cancer (88.7%), including 47 cases classified as low risk. The MRI-guided biopsies identified an additional 16 cases of intermediate/high-risk prostate cancer and led to the reclassification of 13 cases from low risk to intermediate/high risk. Thus, the addition of multiparametric MRI with targeted biopsies for suspicious or equivocal lesions to standard biopsy allowed the identification of clinically significant disease in an additional 13% of the study population.

A single-center trial randomized 130 biopsy-naïve men to a control group that received TRUS-guided random biopsy alone or to a group that received prebiopsy multiparametric MRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion targeted biopsy.[171] 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.[265] 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%; $P < .001$).

In another single-center study, 452 men with no prior biopsy and suspicious regions on multiparametric MRI underwent both systematic biopsy and fusion-targeted biopsy.[266] Systematic biopsies identified more cancer (49.2% vs. 43.5%; $P = .006$), but 82.9% of the 41 cancers detected by systematic biopsy and not by targeted biopsy were Gleason 6. Furthermore, targeted biopsies identified more Gleason 7+ disease (88.6% vs. 77.3%; $P = .037$). Another similar study showed similar results.[267]

In a large single-institution prospective cohort study, 1003 men with elevated PSA or abnormal DRE and lesions visible on multiparametric MRI underwent both MRI/US fusion-targeted and standard biopsy.[174] In this study, 196 men had no prior biopsy, and results appear to be similar in the biopsy-naïve subgroup compared with the entire cohort. Of the full cohort, 170 men had pathology results available following radical prostatectomy: 8 men (4.7%) had intermediate- or high-risk cancers that would have been missed based on targeted biopsy results of no or low-risk cancer and 44 men (26%) had intermediate- or high-risk cancers that would have been missed based on standard biopsy results of no or low-risk cancer. The sensitivities for detection of intermediate- or high-grade cancer of targeted and standard biopsies were 77% and 53%, respectively, whereas the specificities of the 2 approaches were similar at 68% and 66%, respectively. Combining both biopsy techniques increased sensitivity to 85% but decreased specificity to 49%. The effect of targeted biopsies on clinical outcomes is still unknown.

As noted earlier, the results of the PROMIS trial as well as the trial reported by Kasivisvanathan and colleagues showed that the use of MRI and MR targeting in those with an elevated PSA resulted in improved detection rates of clinically significant cancer compared to TRUS-guided biopsy and its use could decrease biopsy rates.[175,176]

Overall, the panel believes that the data for the use of MRI and MRI-targeted biopsies in the initial biopsy setting are insufficient, as yet, to recommend them over standard, US-guided biopsies in this setting at this time. However, data showing that use of MRI may reduce unnecessary biopsies, lower detection of clinically insignificant disease, and better identify high-risk cancers are accumulating. MRI and MRI-targeted biopsies can be considered in the setting of repeat biopsy, as discussed below.

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 saturation biopsy strategies and/or 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 men to inform decisions regarding repeat biopsy (see *Biomarker Testing: PSA Derivatives and Other Tests*, above).

Targeted Biopsy Techniques for Repeat Biopsy

After 1 or more negative TRUS biopsies, men 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.[167,268-274] Reported cancer detection rates by targeted fusion biopsies in men with previous negative biopsies range from 34% to 51%.[167,269-271] Studies that used direct MR guidance for targeted biopsies report similar cancer detection rates in men with previous negative biopsies: 41% to 56%.[272-274]

The targeted biopsy approach may lead to a higher rate of detection of clinically significant cancer in men 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 men 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.[270] Prostate cancer was found in 36 men (34%). In this study, 21 of 23 cancers (91%) identified by targeted biopsy were significant (Gleason 3 + 4 or mean core length ≥4 mm), compared with 15 of 28 cancers (54%) identified by standard biopsy. Targeted biopsies missed 2 cases of clinically significant cancer compared with 5 missed cases with standard biopsies.

Another prospective study included 347 patients with findings suspicious for prostate cancer, many of whom had 1 or more previous negative biopsies.[167] 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 men without MRI-suspicious lesions were diagnosed with intermediate-risk tumors. In this study, the cancer detection rate was 51% in men with previous negative biopsies.

In a prospective study, 583 patients (56% with prior negative biopsy) underwent multiparametric MRI.[275] All men received systematic 12-core biopsies, and men with lesions seen on MRI also received fusion-guided biopsies. Multivariate analysis revealed that a higher MRI suspicious score increased the likelihood of finding Gleason 7+ cancer by 3.3-fold (95% CI, 2.2–5.1; $P < .0001$).

A recent meta-analysis of 16 studies (1926 men) also showed that MRI-targeted biopsy improved detection of clinically significant prostate cancer in men with previous negative biopsies over standard TRUS biopsy.[276] Overall, the panel believes that targeted biopsy techniques may help identify regions of cancer missed on prior biopsies and should be considered in selected cases after at least 1 negative biopsy.[183] They can be considered before or after biomarker tests (discussed above) to aid in patient/clinician discussions.

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. 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 approaches seem to have similar rates of cancer detection.[277] 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; $P = .3$).[278] 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.[279] In fact, recent studies reported zero or near-zero rates of sepsis in men biopsied with the transperineal approach.[280-282] Another possible benefit of the transperineal over the transrectal approach is more accurate staging.[283] However, the transperineal approach may be associated with a higher rate of urinary retention.[279] The transrectal approach can be performed in the office.

A study of transperineal template-guided mapping biopsy found detection rates of 55.5%, 41.7%, and 34.4% for men with 1, 2, and ≥3 previous negative biopsies, respectively.[284] Other groups have reported similar rates of detection using saturation biopsies in men with previous negative biopsies.[282,285,286]

Compared with an extended biopsy approach (12–14 cores), one prospective, non-randomized study found that transrectal saturation biopsy detected significantly more cancers in men with 1 previous negative biopsy (32.7% vs. 24.9%; $P = .0075$).[287] The detection of insignificant cancer did not differ significantly between the groups (40.1% vs. 32.6%; $P = .2$).

Based on this emerging evidence, the panel believes that a saturation biopsy strategy can be considered for very-high-risk men with previous negative biopsies. However, as noted, alternative strategies using MRI or biomarkers (discussed above) may avoid the use of biopsy altogether.

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.[288] 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.[289,290]

In an analysis of 17,472 men in the SEER database, prostate biopsy was associated with a 2.7-fold increased risk of 30-day hospitalization.[291] 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 men who were biopsied, in which the hospitalization rate increased from 1.0% in 1996 to 4.1% in 2005.[292] 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.[293]

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.[294,295] Resistance is associated with prior prophylactic exposure to fluoroquinolone.[296,297] There are additional risks associated with the use of fluoroquinolones, as indicated in the Boxed Warning on the FDA label for these drugs: “These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient.”[298] Although these 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.[299]

Up to 90% of men undergoing a prostate biopsy have reported some discomfort during the procedure.[300] Both topical lidocaine gel and an injectable nerve block have been shown to be safe and efficacious for reducing discomfort.[301,302] 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.[303] Another small trial found the combination of lidocaine with pelvic plexus block to be most effective at relieving pain associated with prostate biopsy.[304]

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.[305] For cases such as men with anal strictures, men 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, race, 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 race (ie, African-American men) 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 men 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 screening is to find aggressive cancers, that screening 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.[306,307]
- 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 men 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 frequency of testing be 2 to 4 years for men aged 45 to 75 years with serum PSA values below 1 ng/mL. For men with PSA of 1 to 3 ng/mL, testing should occur at 1- to 2-year intervals.
- The panel recommends that biopsy should be considered in those aged 45 to 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, race, health status, and patient preference.

- The panel recommends that PSA testing be 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 men unlikely to benefit from prostate cancer diagnosis based on age and/or comorbidity.

- The panel recommends that consideration may be given to biomarkers that improve biopsy specificity such as %f PSA, 4Kscore, and PHI before biopsy in men with serum PSA levels of >3 ng/mL who desire more specificity. These tests, ConfirmMDx, and PCA3 are also options in men being considered for repeat biopsy after an initially benign result. Multiparametric MRI may be of similar value in both situations.

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 men diagnosed with cancer on prostate biopsy, the panel does not recommend routine repeat biopsy, except in special circumstances, such as the suspicion that the patient harbors more aggressive cancer than was evident on the initial biopsy and the patient is otherwise a candidate for active surveillance as outlined in the treatment guidelines.

High-Grade Prostatic Intraepithelial Neoplasia

Approximately 10% of patients undergoing biopsy will be found to have high-grade prostatic intraepithelial neoplasia (HGPIN).[308] 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.[309-311]

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.[312] If extended biopsies were used initially, only those at high risk for more aggressive cancer should undergo repeat biopsy.[313] It is recommended that those with *multifocal* HGPIN be followed as men with atypia suspicious for cancer (see below).[314] Men with *focal* HGPIN should be followed as men with benign results (see below).

Atypia, Suspicious For Cancer

Distinct from HGPIN in which a basal cell layer is present, atypia is characterized by small single-cell layer acini. 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.[315,316]

Therefore, the panel recommends that a repeat biopsy with relative increased sampling of the atypical site be considered in these patients. 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.

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).[317] 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 a 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 screening 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 screening 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).

These NCCN Guidelines for Prostate Cancer Early Detection will incorporate many 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 men 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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