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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer Early Detection

Version 2.2025 — June 24, 2025

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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NCCN Guidelines Version 2.2025
Prostate Cancer Early Detection

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 2.2025 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 1.2025 include:

PROSD-2
• Early detection pathways reformatted for clarity.

PROSD-A
• Prior to initial biopsy:
  ‣ Test added: MyProstateScore 2.0 (MPS2) (category 2B)
  ‣ Test added: Stockholm3
• After initial biopsy:
  ‣ Test added: MPS2 (category 2B)

MS-1
• The discussion has been updated to reflect the changes in the algorithm.

Updates in Version 1.2025 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 2.2024 include:

PROSD-1
• Introduction, paragraph 2 modified as follows:
  ‣ Sentence 1 modified: The guidelines are specifically for individuals with a prostate opting to participate in an early detection program (after receiving the appropriate counseling on the *potential benefits and harms* ~~pros and cons~~).
  ‣ Sentence removed: 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.

PROSD-2
• Risk assessment modified: *Discuss potential benefits and harms of* ~~Start risk and benefit discussion about offering~~ prostate cancer early detection.
• Early detection evaluation pathways extensively revised.

PROSD-2A
• Footnote a, sentence removed: Family cancer history includes, but is not limited to, a first- or second-degree relative with metastatic prostate cancer, ovarian cancer, breast cancer in a relative assigned male at birth, breast cancer diagnosed in a relative assigned female at birth at age ≤45 years, colorectal or endometrial cancer at ≤50 years, or pancreatic cancer or two or more first- or second-degree relatives with breast, prostate (but not clinically localized Grade Group 1), colorectal, or endometrial cancer at any age.
• Footnote b modified: If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. Individuals harboring germline mutations in prostate cancer risk genes may have an elevated lifetime risk of prostate cancer and, in the case of certain genes or mutations, an elevated risk of early-onset and/or potentially lethal prostate cancer (eg, *BRCA2*). ~~Such risk genes include, but are not limited to, *BRCA2, BRCA1, ATM, CHEK2, PALB2, HOXB13, MLH1, MSH2, MSH6, PMS2, EPCAM*, and *TP53*. S~~*For prostate cancer susceptibility genes and cancer risk management based on genetic testing results,* s*ee* NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (GENE-A and BRCA-A). ~~Consequently, prostate cancer early detection is recommended at age 40 years for *BRCA2* carriers, and it is reasonable for individuals with other germline mutations to consider shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year.~~

UPDATES

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Updates in Version 1.2025 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 2.2024 include:

- Footnote d modified: Black/African American individuals have a significantly higher incidence of prostate cancer, ~~increased prostate cancer mortality, and~~ earlier age at diagnosis*, and increased prostate cancer mortality* compared to white individuals. ~~This is~~ *The higher incidence and earlier age at diagnosis are* attributable to a greater *incidence of* ~~risk of developing~~ preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. The survival disparities seen in Black/African American individuals are related to *these factors and to* social determinants of health~~, and~~ lack of access to care, *and treatment disparities,* and not to race itself or differences in the frequency of tumor-acquired genomic variants (Vince RA, et al. JAMA Netw Open 2023;6:e2250416; Schumacher FR, et al. JCO Precis Oncol 2021;5:PO.21.00324). In fact, data show that Black patients who receive equitable prostate cancer treatment have similar outcomes to white patients (Riviere P, et al. Cancer 2020;126:1683-1690). Therefore, there is a need for higher vigilance in this population in the form of appropriate screening and treatment. Although there is currently little evidence to support that screening at an earlier age will result in decreased morbidity and mortality compared to testing at age 45, and earlier screening may increase overdiagnosis (Tsodikov A, et al. Cancer 2017;123:2312-2319), data show that Black individuals benefit more from screening than white individuals (Basourakos SP, et al. NEJM Evid 2022;1:10.1056/evidoa2200031). Therefore, many support the recommendation for Black/African American individuals to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year.
- Footnote g, reference added: Matsukawa A, et al. Eur Urol Oncol 2024;7:697-704.

[PROSD-2B]

- Footnote h, modified: *Prostate cancer early detection is recommended in adults with a prostate aged 45 years (or 40 years if risk factors, see risk assessment on PROSD-2) through 75 years who might have a life expectancy of ≥10 years and who opt to participate in an early detection program. The decision to test beyond 75 years should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy.* Testing after 75 years of age should be done only in very healthy people with little or no comorbidity (especially if they have never undergone PSA testing or have a rising PSA) to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread testing in this population would substantially increase rates of overdetection and is not recommended.
- Footnote j added: Transgender women and other gender-diverse individuals assigned male at birth retain their prostates regardless of gender-affirmation surgery. They should therefore undergo shared decision-making regarding age-appropriate prostate cancer early detection. For those on gender-affirming hormones, such as estrogen, PSA values should be interpreted cautiously bearing in mind the castrating effects of gender-affirming hormones that may drastically decrease PSA levels. One study found a median PSA level of 0.02 ng/mL (interquartile range [IQR] 0–0.2, 95th percentile 0.6 ng/mL) for transgender women with a median age of 60 years who were on estrogen for at least 6 consecutive months and had no known prostate cancer (Nik-Ahd F, et al. JAMA 2024;332:335-337). Clinicians should take this information into account when interpreting PSA values in transgender and other gender-diverse patients undergoing gender-affirming care. Special attention should be paid to rising PSA levels in this population.
- Footnote k modified: Individuals ≥60 years with a PSA <1.0 ng/mL and those >75 years of age with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases in their lifetime. This low risk is especially true for those in the latter category. *The testing interval ranges included on PROSD-2 were not a unanimous decision by the Panel. There are some Panel members who believe that 2-4 years is too long for individuals aged 40-75 years with PSA <1.0 ng/mL. However, the Panel majority supported the intervals as listed.*

[PROSD-3]

- Further evaluation and indications for biopsy, column 2, bullet 2 modified: Consider biomarkers *and/or risk calculators* that improve the specificity of screening.
- Footnote m modified: A negative MRI does not exclude the possibility of cancer. Consider biomarkers*, risk calculators,* and/or PSA density when deciding whether to avoid a biopsy in an individual with a negative mpMRI result. *Biparametric MRI has been shown to offer similar diagnostic quality and can be considered as an alternative to mpMRI in certain contexts. Bosaily AE, et al. Eur Urol 2020;78:503-511; van der Leest M, et al. Eur Urol 2019;76:574-581; Schoots IG, et al. AJR Am J Roentgenol 2021;216:3-19.*

UPDATES

Updates in Version 1.2025 of the NCCN Guidelines for Prostate Cancer Early Detection from Version 2.2024 include:

- Footnote n modified: ~~Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk.~~ Lower percent-free PSA and/or higher PSA density are associated with a greater risk of high-grade prostate cancer. ~~The probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. Extent of validation of these tests across diverse populations is variable. It is not yet known how such tests could be applied in optimal combination with MRI.~~
- Footnote o added: See Principles of Biomarker Testing in Prostate Cancer Early Detection (PROSD-A). (Also for PROSD-4)
- Footnote p, reference added: Haj-Mirzaian A et al. JAMA Netw Open 2024;7:e244258. PROSD-4
- Footnote removed: Tests that improve specificity in the post-biopsy setting—including percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA—should be considered in patients thought to be higher risk despite a negative prostate biopsy (PROSD-3). PROSD-A
- New page added: Principles of Biomarker Testing in Prostate Cancer Early Detection.

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INTRODUCTION

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

The guidelines are specifically for individuals with a prostate opting to participate in an early detection program (after receiving the appropriate counseling on the potential benefits and harms). It is the majority opinion of the Prostate Cancer Early Detection Panel members that there is a growing population of patients currently being diagnosed with prostate cancer who can, and should, be monitored for their disease rather than immediately treated as presented in the NCCN Guidelines for Prostate Cancer. The guidelines are continuously in a state of evolution, and the Panel will incorporate changes based on new evidence and expert opinion and provide a rating of consensus for each recommendation.

Baseline Evaluation (PROSD-2)

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

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NCCN Guidelines Version 2.2025
Prostate Cancer Early Detection

BASELINE EVALUATION

RISK ASSESSMENT

EARLY DETECTION EVALUATION

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

Discuss potential benefits and harms of prostate cancer early detection:
- Baseline PSA[g]
- Consider baseline digital rectal examination (DRE)[g]

Age 45–75 y for patients with average risk

Age 40–75 y for patients with high risk:
- Black/African American individuals[d]
- Those with germline mutations that increase the risk for prostate cancer[a,b,c] (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate)
- Those with concerning family or personal history[a,c]

Age >75 y, in select patients (category 2B)[h]

PSA <1 ng/mL,[e,j] DRE normal (if done) → Repeat testing at 2- to 4-year intervals[k]

PSA 1-3 ng/mL[e,j] and DRE normal (if done) → Repeat testing at 1- to 2-year intervals and For younger patients, consider further evaluation[i] (PROSD-3)

PSA >3 ng/mL[e,i,j] and/or very suspicious DRE → Further Evaluation and Indications for Biopsy (PROSD-3)

PSA ≤3 ng/mL[e,j] and DRE normal (if done) → Repeat testing at 1- to 2-year intervals and For younger patients, consider further evaluation[i] (PROSD-3)

PSA ≥4 ng/mL[e,j] or very suspicious DRE → Further Evaluation and Indications for Biopsy (PROSD-3)

PSA <4 ng/mL,[e,j] DRE normal (if done), and no other indications for biopsy → Consider discontinuing screening if clinically appropriate or Repeat testing at 1- to 3-year intervals[h,k]

Not screened[h]

See footnotes on PROSD-2A and PROSD-2B

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

FOOTNOTES

a Family or personal cancer history and/or family or personal history of high-risk germline mutations can inform when to begin shared decision-making regarding prostate cancer early detection. Patients with a suspicious family history should undergo genetic testing. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (CRIT-1) and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (LS-1). Page EC, Eur Urol 2019;76:831-842; Giri VN, et al. J Clin Oncol 2020;38:2798-2811.

b If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. Individuals harboring germline mutations in prostate cancer risk genes may have an elevated lifetime risk of prostate cancer and, in the case of certain genes or mutations, an elevated risk of early-onset and/or potentially lethal prostate cancer (eg, *BRCA2*). For prostate cancer susceptibility genes and cancer risk management based on genetic testing results, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (GENE-A and BRCA-A).

c If genetic testing does not show the presence of a germline mutation in a prostate cancer risk gene but family history is concerning, shared decision-making is recommended regarding the timing and frequency of PSA testing.

d Black/African American individuals have a significantly higher incidence of prostate cancer, earlier age at diagnosis, and increased prostate cancer mortality compared to white individuals. The higher incidence and earlier age at diagnosis are attributable to a greater incidence of preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. The survival disparities seen in Black/African American individuals are related to these factors and to social determinants of health, lack of access to care, and treatment disparities, and not to race itself or differences in the frequency of tumor-acquired genomic variants (Vince RA, et al. JAMA Netw Open 2023;6:e2250416; Schumacher FR, et al. JCO Precis Oncol 2021;5:PO.21.00324). In fact, data show that Black patients who receive equitable prostate cancer treatment have similar outcomes to white patients (Riviere P, et al. Cancer 2020;126:1683-1690). Therefore, there is a need for higher vigilance in this population in the form of appropriate screening and treatment. Although there is currently little evidence to support that screening at an earlier age will result in decreased morbidity and mortality compared to testing at age 45, and earlier screening may increase overdiagnosis (Tsodikov A, et al. Cancer 2017;123:2312-2319), data show that Black individuals benefit more from screening than white individuals (Basourakos SP, et al. NEJM Evid 2022;1:10.1056/evidoa2200031). Therefore, many support the recommendation for Black/African American individuals to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year.

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

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

g The best evidence supports the use of serum PSA for the early detection of prostate cancer. DRE should not be used as a stand-alone test. DRE can be considered as a baseline test in addition to serum PSA in all patients, but has its greatest usefulness in those with elevated PSA. Consider referral for biopsy or further testing if DRE is suspicious for cancer at any PSA level. Halpern JA, et al. J Urol 2018;199:947-953; Arsov C, et al. Int J Cancer 2022;150:1861-1869; Matsukawa A, et al. Eur Urol Oncol 2024;7:697-704.

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

FOOTNOTES

h Prostate cancer early detection is recommended in adults with a prostate starting at age 45 years (or 40 years if risk factors, see risk assessment on PROSD-2) through 75 years who might have a life expectancy of ≥10 years and who opt to participate in an early detection program. The decision to test beyond 75 years should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. Testing after 75 years of age should be done only in very healthy people with little or no comorbidity (especially if they have never undergone PSA testing or have a rising PSA) to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread testing in this population would substantially increase rates of overdetection and is not recommended.

i The median PSA values for those aged 40–49 years range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Individuals who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk. Further evaluation (PROSD-3) can be considered for patients who have PSA levels that are above the median for their age group, even if they do not meet the threshold of >3 ng/mL.

j Transgender women and other gender-diverse individuals assigned male at birth retain their prostates regardless of gender-affirmation surgery. They should therefore undergo shared decision-making regarding age-appropriate prostate cancer early detection. For those on gender-affirming hormones, such as estrogen, PSA values should be interpreted cautiously bearing in mind the castrating effects of gender-affirming hormones that may drastically decrease PSA levels. One study found a median PSA level of 0.02 ng/mL (interquartile range [IQR] 0–0.2, 95th percentile 0.6 ng/mL) for transgender women with a median age of 60 years who were on estrogen for at least 6 consecutive months and had no known prostate cancer (Nik-Ahd F, et al. JAMA 2024;332:335-337). Clinicians should take this information into account when interpreting PSA values in transgender and other gender-diverse patients undergoing gender-affirming care. Special attention should be paid to rising PSA levels in this population.

k Individuals ≥60 years with a PSA <1.0 ng/mL and those >75 years of age with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases in their lifetime. This low risk is especially true for those in the latter category. The testing interval ranges on PROSD-2 were not a unanimous decision by the Panel. There are some Panel members who believe that 2-4 years is too long for individuals aged 40-75 years with PSA >1.0 ng/mL. However the Panel majority supported the intervals as listed.

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NCCN Guidelines Version 2.2025
Prostate Cancer Early Detection

NCCN Guidelines Index
Table of Contents
Discussion

FURTHER EVALUATION AND INDICATIONS FOR BIOPSY[l]

MANAGEMENT

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

→

- **Multiparametric MRI (mpMRI) (category 1) if available[m]**
- **Consider biomarkers and/or risk calculators that improve the specificity of screening[n,o]**

High suspicion for clinically significant cancer[m,n,p] → **Image-guided biopsy via transrectal or transperineal approach[q] with MRI targeting (preferred) or without MRI targeting[r]** → **Management of Biopsy Results (PROSD-4)**

Low suspicion for clinically significant cancer[m,n,p] → **Follow-up in 6–12 mo with PSA/DRE[p]**

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

[m] A negative MRI does not exclude the possibility of cancer. Consider biomarkers, risk calculators, and/or PSA density when deciding whether to avoid a biopsy in an individual with a negative mpMRI result. Biparametric MRI has been shown to offer similar diagnostic quality and can be considered as an alternative to mpMRI in certain contexts. Bosaily AE, et al. Eur Urol 2020;78:503-511; van der Leest M, et al. Eur Urol 2019;76:574-581; Schoots IG, et al. AJR Am J Roentgenol 2021;216:3-19.

[n] Lower percent-free PSA and/or higher PSA density are associated with a greater risk of high-grade prostate cancer.

[o] Principles of Biomarker Testing in Prostate Cancer Early Detection (PROSD-A).

[p] Patients with a persistent and significant increase in PSA should be encouraged to undergo biopsy, including patients with a higher PSA density, even if they have a normal MRI. Haj-Mirzaian A et al. JAMA Netw Open 2024;7:e244258.

[q] A transperineal approach to transrectal ultrasound (TRUS) biopsy may be associated with a lower risk of sepsis and a reduced need for antibiotics compared to a transrectal approach.

[r] In patients undergoing biopsy, targeting using MRI/ultrasound fusion significantly increases the detection of clinically significant, higher-risk (Grade Group ≥3) disease while lowering the detection of lower-risk (Grade Group 1 or lower-volume Grade Group 2) disease. It is strongly recommended that image-guided biopsy techniques be employed routinely. Radiologic expertise and the use of high-quality mpMRI hardware is essential for optimal interpretation of scans. Most advocate for a combined targeted and systematic biopsy approach as some high-grade cancers are uniquely detected using the systematic approach and systematic biopsies are needed for risk stratification if cancer is found. However, some advocate for excluding systematic biopsy in those undergoing MRI targeting due to concerns that it may increase the risk of overdiagnosis. Siddiqui MM, et al. JAMA 2015;313:390-397; Ahmed HU, et al. Lancet 2017;389:815-822; Kasivisvanathan V, et al. N Engl J Med 2018;378:1767-1777; Drost FH, et al. Eur Urol 2020;77:78-94; Ahdoot M, et al. N Engl J Med 2020;382:917-928; Rouvière O, et al. Lancet Oncol 2019;20:100-109; van der Leest M, et al. Eur Urol 2019;75:570-578.
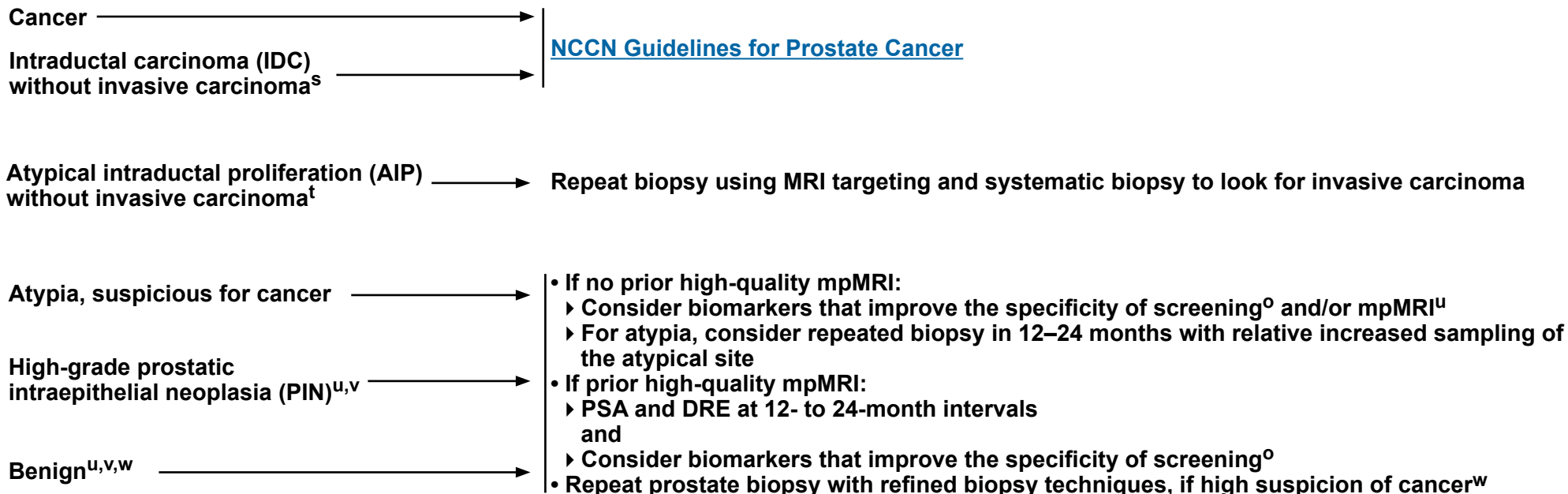
Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF BIOPSY RESULTS

Cancer ⟶

Intraductal carcinoma (IDC) without invasive carcinoma[s] ⟶ **NCCN Guidelines for Prostate Cancer**

Atypical intraductal proliferation (AIP) without invasive carcinoma[t] ⟶ Repeat biopsy using MRI targeting and systematic biopsy to look for invasive carcinoma

Atypia, suspicious for cancer ⟶

High-grade prostatic intraepithelial neoplasia (PIN)[u,v] ⟶

Benign[u,v,w] ⟶

- **If no prior high-quality mpMRI:**
  - ▸ **Consider biomarkers that improve the specificity of screening[o] and/or mpMRI[u]**
  - ▸ **For atypia, consider repeated biopsy in 12–24 months with relative increased sampling of the atypical site**
- **If prior high-quality mpMRI:**
  - ▸ **PSA and DRE at 12- to 24-month intervals and**
  - ▸ **Consider biomarkers that improve the specificity of screening[o]**
- **Repeat prostate biopsy with refined biopsy techniques, if high suspicion of cancer[w]**

[o] Principles of Biomarker Testing in Prostate Cancer Early Detection (PROSD-A).

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

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

[u] It is well known that a negative prostate biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. Patients with negative prostate biopsies should be followed with DRE and PSA with consideration of mpMRI and biomarker tests that improve the specificity of PSA testing.

[v] PSA testing may be discontinued at certain ages and PSA cutpoints. See Discussion.

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

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

NCCN Guidelines Version 2.2025
Prostate Cancer Early Detection

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PRINCIPLES OF BIOMARKER TESTING IN PROSTATE CANCER EARLY DETECTION

- Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to more precisely estimate risk.
- Biomarker tests should meet the following criteria of both validity and clinical utility to be included in the NCCN Guidelines for Prostate Cancer Early Detection:
  ‣ Test should be validated in a patient cohort that is representative of the intended-use population, ideally in a multi-site, prospective, external validation study or multiple single-site studies.
  ‣ Studies should clearly and transparently describe the eligible patient population and how patients were selected for the study.
  ‣ Validation study or studies should be appropriately powered to achieve statistical significance (on the order of hundreds of patients or more, rather than tens of patients).
  ‣ Study populations should ideally reflect the racial and ethnic diversity of the target population, and studies should report racial and ethnic composition.
  ‣ Validation studies should report most, or all, of the measures listed below (acceptable thresholds are <u>underlined</u>). Reports of receiver operating characteristic (ROC) and area under the curve (AUC) measures alone are not adequate, because these measures are difficult to interpret and they do not describe performance in relation to any specific clinical cut-off.
    ◊ Number of patients with clinically significant prostate cancer (currently defined as Grade Group ≥2) diagnosed with the test above a specific test cut-off compared to without the test (PSA alone) at specific test cutoff
      – <u>Maintained detection (non-inferior to PSA)</u>
      – <u>Missed/delayed clinically significant diagnoses, <10%</u>
    ◊ Number of patients with clinically insignificant prostate cancer (GG 1) found with the test and without the test (PSA alone) above and at a specific test cutoff
      – <u>Reduction in clinically insignificant cancers, >50%</u>
      – <u>Ratio of reduction in clinically insignificant to missed/delayed clinically significant diagnoses, ≥2</u>
    ◊ Number of biopsies performed in individuals with the test above a specific test cut-off compared to without test (PSA alone)
      – <u>Unnecessary biopsies avoided, >30%</u>
- Prior to initial biopsy: The probability of high-grade cancer (Grade Group ≥2) may be further defined prior to initial biopsy utilizing tools such as the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), MPS 2.0 (MPS2) (category 2B), Stockholm3, and IsoPSA.
- After initial biopsy: Tests that improve specificity in the post-biopsy setting may be considered in patients thought to be higher risk despite a negative prostate biopsy. Tests to be considered are percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, MPS2 (category 2B), and IsoPSA.
- The extent of validation of these tests across diverse populations is variable.
- It is not yet known how such tests could be applied in optimal combination with MRI.

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

ABBREVIATIONS

AIP	atypical intraductal proliferation
AUC	area under the curve
DRE	digital rectal examination
H&P	history and physical
IDC	intraductal carcinoma
IQR	interquartile range
mpMRI	multiparametric MRI
MPS	MyProstateScore
PCPT	Prostate Cancer Prevention Trial
PHI	Prostate Health Index
PIN	prostatic intraepithelial neoplasia
PSA	prostate-specific antigen
ROC	receiver operating characteristic
TRUS	transrectal ultrasound

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

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

Discussion

This discussion corresponds to the NCCN Guidelines for Prostate Cancer Early Detection. Last updated: June 23, 2025

Table of Contents

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 Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer Early Detection provide a set of sequential recommendations detailing an early detection and evaluation strategy for maximizing the detection of prostate cancer that is effectively treatable and that, if left undetected, represents a risk to the patient. At the same time, these guidelines focus on minimizing unnecessary procedures and limiting the detection of indolent disease. The overall goals of these guidelines are to reduce suffering and death from prostate cancer while also limiting morbidity from unnecessary biopsies, overdiagnosis, and overtreatment.

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

Overview

Prostate cancer is the most commonly diagnosed cancer, contributing to 30% of all new diagnoses in males, and is the second leading cause of cancer deaths in American men.[1] In 2025, it is estimated that 313,780 Americans will be diagnosed with prostate cancer and 35,770 will die of this disease.[1] During the same period, nearly 20 million individuals in the United States will be confronted with important decisions regarding early detection for prostate cancer. Men in the United States have about 1 chance in 8 (12.9%) of eventually being diagnosed with this malignancy and about 1 chance in 41 (2.4%) of eventually dying of it.[2] From 1993 to 2018, death rates from prostate cancer in the United States fell by 53%, largely due to early detection and improved treatment, although death rates stabilized in the last few years of that period.[1,3]

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

Guidelines Update Methodology

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Prostate Cancer Early Detection, an electronic search of the PubMed database was performed to obtain key literature in the field of prostate cancer early detection using the following search terms: (prostate cancer) AND

(screening OR early detection). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes 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 II; Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[5] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men, women, female, and male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in

future studies and organizations to use more inclusive and accurate language in their future analyses.

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 value that prompts evaluation. One study showed that approximately 25% of individuals with initial PSA levels between 4 and 10 ng/mL had normal PSA values upon repeat testing.[6]

PSA is not a cancer-specific marker, and as such most individuals with elevated PSA levels do not have prostate cancer. The risk of prostate cancer increases with increasing PSA, but there is no level of PSA below which the risk of prostate cancer can be eliminated. Total PSA (tPSA) levels >10 ng/mL confer a >67% likelihood of biopsy-detectable prostate cancer, and only about 18% of patients with PSA in the 4 to 10 ng/mL range have a subsequent positive biopsy.[7,8] Still, individuals with low PSA values have a significant chance of having prostate cancer. Using data from 18,882 participants in the Prostate Cancer Prevention Trial (PCPT), Thompson et al demonstrated that 15% of those with a PSA level of ≤4.0 ng/mL and a normal digital rectal examination (DRE) had prostate cancer (as diagnosed by end-of-study biopsies).[9] The PCPT investigators

determined the sensitivity and specificity of PSA levels for detecting any prostate cancer using various cut-offs. At 3.1 ng/mL, PSA has a sensitivity of about 32% and a specificity of about 87%.[10]

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.[11] 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.[12]

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

Factors Affecting PSA Levels
PSA can be elevated due to infection, recent instrumentation, ejaculation, or trauma. However, empiric antibiotic use appears to have little value for improving test performance in asymptomatic patients with an elevated PSA.[13]

The 5α-reductase inhibitors (5-ARIs) finasteride and dutasteride are commonly used to treat lower urinary tract symptoms due to benign prostatic hyperplasia (BPH). Use and duration of 5-ARI therapy should be elicited carefully in the medical 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.[14] However, this effect is tremendously variable. For example, one study showed that after 12 months of treatment, only 35% of patients demonstrated the expected 40% to 60% decrease in PSA, while another 30% had a >60% decrease.[15] Thus, the commonly used method of doubling the measured PSA value to obtain an adjusted value may result in unreliable cancer detection.

In fact, if a significant PSA decrease does not occur while taking 5-ARIs, it 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.[16-18] Although reflex ranges for PSA among patients on 5-ARIs have not been established, a confirmed rise from post-5-ARI treatment nadir may be a better indication for biopsy than doubling the PSA level.

The PCPT of 18,882 participants demonstrated that finasteride reduced the incidence of prostate cancer by 25% compared to placebo.[19] The decreased risk persisted at 21% through 16 years of follow-up.[20] This reduction was almost exclusively for low-grade (Grade Group 1) tumors; an increased proportion of aggressive (Grade Group ≥2) tumors was seen. However, after 18 years of follow-up, there was no significant difference in overall survival or survival after the diagnosis of prostate cancer in those on finasteride compared to the control group.[21] In addition, after a median follow-up of 18.4 years, fewer deaths due to prostate cancer were seen in the finasteride group.[22] Although this difference was not statistically significant, the results suggest that earlier fears that finasteride use would lead to an increase in prostate cancer mortality were unfounded.

In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, PSA detected more high-grade tumors in the dutasteride arm, while the overall prostate cancer diagnosis fell by 23% compared to the control arm.[16] Similar to the PCPT trial, the difference in the number of high-grade cancers detected did not result in a mortality difference.[23]

A report on the CombAT trial also showed a 40% lower incidence of prostate cancer with dutasteride plus tamsulosin (another BPH drug) compared to tamsulosin alone, along with a slightly improved yield of PSA-driven biopsy.[18] Unlike the PCPT and REDUCE studies, diagnosis of high-grade (Grade Group ≥2) tumors was not increased.

A population-based prospective study using data from 333,820 participants in the Stockholm PSA and Biopsy Register and Prescribed Drug Register found that 5-ARI exposure decreased the risk for prostate cancer overall and for prostate cancer of Grade Group ≤3, with longer courses resulting in a larger decreased risk.[24] Grade Group 4–5 prostate cancer risk was unaffected by 5-ARI treatment.

Overall, these studies suggest that PSA testing may have enhanced specificity for patients receiving finasteride or dutasteride. However, in a population-based cohort study, researchers analyzed >80,000 records of patients with prostate cancer and found that use of 5-ARI before diagnosis was associated with delayed diagnosis, higher stage at diagnosis, higher prostate cancer–specific mortality, and higher all-cause mortality.[25] Whether or not individuals should consider taking these agents for chemoprevention is beyond the scope of this guideline.

It should also be noted that finasteride at 1 mg/day used to treat male-pattern baldness also lowers serum PSA.[14]

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

A health survey on 12,457 people visiting a prostate cancer screening clinic showed that >20% took herbal supplements, while only 10% took a prescription medication (such as finasteride) to help treat lower urinary tract symptoms.[27] 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.[28-33] 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.[34,35] This trend has likely, but not positively, contributed to a substantial reduction in prostate cancer mortality.[36,37]

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 disease that would not be a problem for the patient if undetected or untreated and that would not have been identified without screening. These arguments hold that overdetection may lead to overtreatment, which is aggressive treatment in individuals with a low probability of yielding clinical benefit. However, analyses of trends in prostate cancer management show that the rates of active surveillance for early-stage disease have increased significantly, allaying initial concerns about overtreatment.[38] 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.[39] After this recommendation, prostate cancer screening decreased, as did biopsy rates, diagnoses of localized prostate cancers, and radical prostatectomy rates.[40-51] The effect of the 2012 USPSTF recommendations on the rate of metastatic prostate cancer diagnoses is, however, unclear, with some studies showing an increase and others showing none.[45,46,52-54]

The USPSTF released updated recommendations in 2018 based on an evidence report and systematic review.[55,56] The recommendations are: 1) against PSA-based prostate cancer screening in individuals aged ≥70 years; and 2) for individualized, informed decision-making regarding prostate cancer screening in individuals aged 55 to 69 years. For those in the latter age group, clinicians should inform them regarding the potential harms and benefits of PSA-based screening. The USPSTF statement does not provide guidance for people <55 years. Data suggest that PSA testing rates increased after this update, reversing previous trends.[57]

DRE

DRE should not be used as a stand-alone method for the early detection of prostate cancer, because DRE alone misses a substantial number of clinically significant cancers.[58] In addition, prostate cancers detected solely by DRE are less likely to be confined to the prostate than those detected through PSA testing, and the positive predictive value (PPV) for DRE alone is poor.[59-63]

Data from the first screening round of the PROBASE trial confirmed that the use of DRE alone is ineffective in the early diagnosis of prostate cancer.[64] The trial included 46,642 participants aged 45 years who were randomized to receive upfront baseline PSA screening, or upfront DRE with baseline PSA screening at 50 years. Of the 23,301 participants who received upfront PSA screening, 186 individuals (0.80%) had a PSA value ≥3 ng/mL (after a second, confirmatory screening) and 120 participants of the 0.8% then underwent biopsy. Prostate cancer was diagnosed in 48 individuals (detection rate, 0.2%), of which four participants were diagnosed with Grade Group ≥3 prostate cancer. Of the 23,194 participants in the delayed PSA screening arm, 6537 accepted and underwent upfront DRE, which resulted in 57 suspicious results, 37 biopsies, and two confirmed Grade Group 1 prostate cancer diagnoses.

DRE With PSA Testing

The use of baseline DRE as part of an early detection program is controversial. Although the absolute numbers may be small, some clinically significant cancers may be missed using a serum PSA cut point alone. In a trial of approximately 36,000 participants, 3568 of them were diagnosed with prostate cancer, and 2233 participants underwent radical prostatectomy.[65] Of these 2233 patients, 303 (14%) were diagnosed by DRE alone, including 60 (3%) with non-organ–confined disease and 56 (3%) with clinical Grade Group >2. Thus, the number of clinically significant prostate cancers found by DRE in individuals with PSA <3 ng/mL is possibly around 0.2% of all individuals screened. In fact, in an analysis of 166,104 individuals with prostate cancer diagnosed between 2004 and 2007 from the SEER database, 685 (0.4%) had palpable, PSA-occult (PSA level of <2.5 ng/mL), Grade Group ≥4 prostate cancer.[66]

In the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, DRE was used in conjunction with PSA in 35,350 participants.[67] Among those with an abnormal DRE, 15.4% also had an elevated PSA. On multivariate analysis, a suspicious DRE was associated with an increased risk of clinically significant prostate cancer (hazard ratio [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; $P = .002$). 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; $P < .001$). The cancer detection rate was higher when both tests were used than when PSA was used alone.

A prospective clinical trial in 6630 individuals directly compared the efficacy of PSA and DRE in the early detection of prostate cancer.[61] The cancer detection rates were 3.2% for DRE, 4.6% for PSA, and 5.8% for DRE plus PSA. Furthermore, among 5519 participants in the control arm of the PCPT, Thompson and colleagues[68] 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.

Evidence suggests that the utility of DRE may be greatest in those with an elevated PSA. An analysis of the PLCO trial found that a suspicious DRE was associated with the identification of Grade Group ≥2 prostate cancer in those with a PSA ≥3 ng/mL (23.0% risk at 10 years vs. 13.7% risk at 10 years in those with a non-suspicious DRE), but not in those with a PSA <2 ng/mL (1.5% vs. 0.7%).[69] Ten-year risk in those with a PSA in the 2 to 3 ng/mL range were 6.5% in individuals with a suspicious DRE compared with 3.5% in individuals with a non-suspicious DRE. Gosselaar and colleagues[70] also showed that among those with a serum PSA >3 ng/mL, those with a positive DRE were more likely to have prostate cancer. Overall, the PPV of a DRE in individuals with a normal PSA is poor (about 4%–21%).[61-63,71]

Considering these data, the Panel recommends DRE as a complementary test that can be considered with serum PSA in asymptomatic individuals who had a risk/benefit discussion and decided to pursue screening for prostate cancer. Since the PPV of a DRE in those with a normal PSA is poor, an abnormal DRE result alone as an indication for biopsy would lead to a large number of unnecessary biopsies and the detection of many insignificant cancers in individuals with low PSA values. Those with a DRE that is very suspicious for cancer should undergo further evaluation regardless of PSA results.

As noted in the data described above, the greatest usefulness of DRE is in those with elevated PSA. Thus, DRE should be performed for anyone with an elevated PSA to aid in decisions regarding biopsy (see *Pre-Biopsy Workup*, below).

Population-Based Screening Studies

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

ERSPC Trial

The ERSPC trial involved about 182,000 participants between the ages of 50 and 74 years in seven European countries, randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening; DRE or other ancillary tests were also performed in the screening group.[72,73] The predefined core group included 162,388 participants aged 55 to 69 years. Death from prostate cancer was the primary outcome. During a median follow-up of 11 years, the cumulative incidence of prostate cancer was 7.4% in the screening group versus 5.1% in the control group. There were 299 prostate cancer deaths in the screening group compared to 462 in the control group. The rate ratio for death from prostate cancer was 0.79 for the screening arm compared to the control arm (95% CI, 0.68–0.91; *P* = .001). The investigators concluded that the PSA-based screening program reduced mortality from prostate cancer by 21%. At the time of publication, the authors stated that 1055 individuals would need to be screened and 37 additional individuals would need to be treated over 11 years to prevent one prostate cancer death. Modeling the ERSPC data, however, Heijnsdijk and colleagues[74] 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 participants diagnosed with prostate cancer in the screening arm and 6107 diagnosed in the control arm, confirmed these results.[75] The unadjusted rate ratio for death from prostate cancer was 0.79 (95% CI, 0.69–0.91) at 13 years. After adjusting for non-participation, the rate ratio of prostate cancer death was 0.73 (95% CI, 0.61–0.88). The authors reported that, for 781 individuals invited for screening or 27 additional prostate cancers

detected, one prostate cancer death could be averted. Furthermore, another analysis of these 13-year data found that fewer participants were diagnosed with metastatic disease in the screening arm (incidence rate ratio, 0.60; 95% CI, 0.52–0.70).[76] After longer follow-up (16 years), the number invited for screening and the number of prostate cancers detected to avert one prostate cancer death were reduced to 570 and 18, respectively.[77]

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%.[78] This same group found that if one controlled for contamination and nonattendance, the risk of death due to prostate cancer could be reduced by up to 51%.[79]

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.[80]

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.[81] Twenty thousand individuals aged 50 to 64 years were randomized to either a screening group invited for PSA testing every 2 years until the age of 69 years or to a control group. In those randomized to screening, 76% attended at least one test. PSA testing in the general population was very low at the beginning (3%) but increased over time. During a median follow-up of 14 years, 1138 participants in the screening group and 718 in the control group were diagnosed with prostate cancer, resulting in a cumulative prostate cancer incidence of 12.7% in the screening group and 8.2% in the control group (HR, 1.64; 95% CI, 1.50–1.80; $P < .0001$). The rate ratio for death from prostate cancer was 0.56 (95% CI, 0.39–0.82; $P = .002$) in the screening group compared with the control group. Overall, 293 individuals needed to be screened and 12 needed to be diagnosed to prevent one

prostate cancer death over 14 years. This study shows that prostate cancer screening is acceptable to the Swedish population and that prostate cancer mortality was reduced almost by half over 14 years. In addition, it should be noted that a cause-specific survival benefit was noted despite the fact that not all cancers were immediately treated. This result suggests that early detection combined with selective treatment based on risk can lower mortality rates without uniform treatment of all cancers.

Eighteen-year follow-up of the Göteborg trial was reported, with 1396 participants diagnosed with prostate cancer in the screening arm and 962 diagnosed in the control arm.[82] The reduction in absolute prostate cancer-specific mortality was 0.72 (95% CI, 0.50–0.94). The number needed to invite to prevent one death was 139 and the number needed to diagnose was 13.

There are several possible explanations for the more favorable results of the Göteborg trial compared to the PLCO (see below) or ERSPC trials. First, the patients were younger and less likely to have incurable prostate cancer at first screening; second, there was less contamination of the control arm because PSA testing was uncommon in the Swedish population when the study began; third, a lower PSA threshold was used for recommending a biopsy; and finally, participants were screened more frequently than in ERSPC and for a longer period than in PLCO. However, because more than half of the participants were included in the main analysis of ERSPC, the Göteborg trial should not be interpreted as a true independent confirmatory study. An analysis of the Göteborg trial showed that the risks of aggressive prostate cancer and prostate cancer mortality became similar in the screening and control arms 9 years after screening cessation.[83]

PLCO Trial

The PLCO study randomized 76,685 individuals aged 55 to 74 years at 10 U.S. study centers to annual screening (annual PSA for 6 years and DRE for 4 years) or usual care.[84] 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 (relative risk [RR], 1.09; 95% CI, 0.87–1.36). Results were similar after 15-year follow-up.[85]

Despite the large sample size, this trial was flawed both by prescreening and the high contamination rate of 40% to 52% per year in the control group (ie, 74% of participants in the usual care arm were screened at least once). The high contamination rates have been confirmed by others.[86,87] 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.[88]

An analysis, which endeavored to account for the increased screening and diagnostic workup in the control arms of the PLCO and ERSPC, found that PSA screening lowered the risk for prostate cancer death in both trials by similar amounts (by an estimated 25%–31% in PLCO and by an estimated 27%–32% in ERSPC).[89]

In a subset analysis of PLCO reported by Crawford and colleagues,[90] a 44% decrease in the risk of prostate cancer-specific death was observed in those with no or minimal comorbidity assigned to screening compared to control, and the numbers needed to screen and treat to prevent one death were 723 and 5, respectively. This benefit was not found among individuals with one or more significant comorbidities. These results suggest that screening is more useful among individuals in good health due to the lack of competing cause for mortality. However, others suggest that such analysis is prone to major methodologic errors.[91]

CAP Trial

The results of the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) were reported in 2018.[92] Participants 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. In a median 15-year follow-up analysis of the same trial, however, a statistically significant reduction in prostate cancer mortality of 0.09% compared to the control group was evident (0.69% vs. 0.78%; P = .03).[93] Although this trial had several very important strengths, it had limitations as well. Only a single PSA test was used, a standard 10-core biopsy was undertaken, there was very little representation of Black individuals, and only 40% of participants completed the intervention (biopsy). Serial testing, higher rates of biopsy completion, longer follow-up, and use of additional technology preceding biopsy (discussed below) may have led to greater benefit with PSA testing.

ProScreen Trial

The ProScreen trial, which randomized 60,745 individuals to compare the incidences of low-grade and high-grade prostate cancers, utilized a 1:3 allocation to either an invitation for screening (intervention) or no invitation for screening (control) group.[94] If PSA level of 3 ng/mL was detected, participating individuals would then undergo 4K risk score testing (see

Biomarker Testing, below). 4K risk scores ≥7.5% led to individuals undergoing prostate gland MRIs, followed by targeted biopsy if MRI-positive. After a 3.2-year median follow-up period, the number of detected lower-grade and high-grade prostate cancers were greater for the invited screening group (0.26% and 1.13%, respectively) compared to those in the non-invited group (0.14% and 0.62%, respectively).

Trial Limitations

In addition to the limitations of the PLCO trial noted previously, these randomized controlled trials (RCTs) also share at least three additional limitations. First, they did not address the potential benefit of screening in those with high-risk factors. For instance, <5% of PLCO participants were of African descent and only 7% reported a family history of prostate cancer.[95] Therefore, it is not known whether individuals at higher risk may benefit more from screening than those at lower risk. Second, many individuals in these studies underwent sextant prostate biopsies rather than extended core biopsies, the standard diagnostic technique used today. Third, the ERSPC may have underestimated benefit due to advanced age at first PSA test (median >60 years), low intensity of screening (largely every 4 years) and, perhaps, suboptimal treatment available in Europe in the 1990s compared to what is available today.

The reduction in prostate cancer mortality must be balanced against the adverse effects of treatment, emphasizing the importance of selective rather than universal treatment of individuals with prostate cancer identified by screening.[74]

Practical Considerations of Testing

Age at Which to Initiate Testing

Controversy exists as to the ideal age to begin screening for prostate cancer. Randomized trials looking at the impact of screening on prostate cancer mortality have focused primarily on individuals aged 55 to 69 years. The ERSPC and Göteborg trials reported decreased disease-specific mortality in individuals aged 55 to 69 and 50 to 64 years, respectively. These results support baseline PSA testing in individuals aged 50 to 55 years with the strongest evidence supporting testing at age 55 years. Analyses of PSA testing in Swedish individuals aged 50 to 54 years support screening in this age group.[96]

As individuals <50 years were not included in these screening studies, baseline testing at earlier ages has not been evaluated in RCTs. However, observational evidence suggests that baseline testing of individuals in their 40s and early 50s may have value for future risk stratification, although some would describe the value as marginal.[97] A study by Lilja and colleagues[98] assessed blood collected from 21,277 participants in Sweden aged 33 to 50 years who were followed until 2006. Among the 1312 patients with prostate cancer and 3728 control participants without prostate cancer, these investigators reported that a single PSA test before age 50 years predicted subsequent prostate cancer up to 30 years later with a robust area under the curve (AUC) of 0.72 (0.75 for advanced prostate cancer). However, the possible risks of unnecessary biopsies and prostate cancer overdetection should be acknowledged with earlier initiation of screening.[99]

Another report clarified associations of age with the long-term risks of metastases.[100] In this study, the risk of prostate cancer death was strongly correlated with baseline PSA in individuals aged 45 to 49 years and 51 to 55 years; 44% of the deaths in the analytic cohort occurred in participants in the highest tenth of the distribution of PSA, suggesting that there may be a strong rationale for baseline testing in those <55 years.

In a nested case-control study of individuals 40 to 59 years of age in the Physicians' Health Study, baseline PSA strongly predicted lethal prostate cancer later in life.[101] For example, those aged 55 to 59 years with PSA levels above the 90th percentile had an odds ratio (OR) of 6.9 (95% CI,

2.5–19.1) for lethal prostate cancer compared with those whose PSA levels were at or below the median. A secondary analysis of a cohort in the PLCO trial also found a strong correlation between baseline PSA levels in participants aged 55 to 60 years and the actuarial 13-year incidence of clinically significant prostate cancer.[102] Those with baseline PSA levels of ≤0.49 ng/mL, 0.50–0.99 ng/mL, 1.00–1.99 ng/mL, 2.00–2.99 ng/mL, 3.00–3.99 ng/mL, and ≥4.00 ng/mL had incidence rates of 0.4% (95% CI, 0%–0.8%), 1.5% (95% CI, 1.1%–1.9%), 5.4% (95% CI, 4.4%–6.4%), 10.6% (95% CI, 8.3%–12.9%), 15.3% (95% CI, 11.4%–19.2%), and 29.5% (95% CI, 24.2%–34.8%), respectively (all pairwise log-rank *P* ≤ .004).

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

Most Panel members favor informed testing beginning at age 45 years for patients with an average risk of developing prostate cancer. Patients considered at high risk for the development of prostate cancer (Black/African American individuals, those with germline mutations linked to the development of prostate cancer, and those with a concerning family or personal history) should consider shared decision-making regarding early detection at age 40. Repeat testing intervals are discussed below.

Frequency of Testing

The ideal screening interval to maximize mortality reduction yet minimize overdiagnosis remains uncertain.

A comparison of two centers involved in the ERSPC trial studied the impact of different screening intervals on the diagnosis of interval cancers in participants aged 55 to 64 years.[103] The Göteborg arm randomized 4202 participants to screening every 2 years, while the Rotterdam arm randomized 13,301 participants to screening every 4 years with similar follow-up of 11 to 12 years. Compared to screening every 4 years, there was a significant 43% reduction in the diagnosis of advanced prostate cancer (clinical stage >T3a, N1, or M1; PSA >20 ng/mL; Grade Group 5 at biopsy) for screening every 2 years. However, there was also a 46% increase in the diagnosis of low-risk prostate cancer (clinical stage T1c, Gleason <6, and PSA <10 ng/mL at biopsy) for screening every 2 years.

Some studies have addressed the effect of PSA levels on the interval of testing, and it appears that individuals with a very low PSA could safely extend the testing interval. In the Rotterdam section of the ERSPC trial, participants with a PSA <1 ng/mL had a very low risk for cancer at 4 and 8 years (0.23% and 0.49%).[104] Other studies have shown that PSA values at younger ages strongly predict the development of or death from prostate cancer.[105,106] For example, in a Swedish case-control study of 1167 individuals, those aged 60 years with PSA concentrations of ≤1 ng/mL had only a 0.5% risk of metastasis by age 85 and a 0.2% risk of death from prostate cancer.[106] Other analyses, some with racially and ethnically diverse cohorts, show a similar correlation with a very low risk of prostate cancer diagnoses, metastases, and death for those with PSA levels in the lower percentiles for their age.[100-102,105,107,108] Overall, the available data show that individuals who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.

In another study, the unscreened Malmö cohort was compared to a cohort with regular screening.[109] The authors concluded that the harms of testing outweigh the benefits for those with PSA <1 ng/mL at age 60 years (approximately 50% of the population). The authors estimated that PSA testing every 2 years in individuals with a PSA <1 ng/mL would result in

171 additional diagnoses per 10,000 individuals in 15 years without a concomitant reduction in prostate cancer mortality.

Microsimulation models suggest that PSA-based screening intervals (with less frequent screening in those with low PSAs) could substantially reduce the testing burden while preserving the lives saved.[110] Another study using microsimulation models of prostate cancer incidence and mortality predicted that a strategy that utilizes biennial intervals for those with average PSA levels and longer screening intervals (every 5 years) for those with low PSA levels (below median for age by decade) allows a 2.27% risk of prostate cancer death compared to 2.86% from no screening.[111] 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.

There is also some evidence that shorter testing intervals may be justified in patients who are at higher risk for the development of prostate cancer. For example, a modeling study looked at the effects of different PSA intervals in Black individuals.[112] The study showed that a shorter interval could reduce mortality without increasing the risk of overdiagnosis in Black people.

After considering these data, the Panel concluded that tailoring screening intervals based on PSA and risk levels might maximize survival advantage while decreasing the number of screenings and limiting overdiagnosis. The Panel recommends repeat testing at 2- to 4-year intervals for individuals with average risk and a PSA <1 ng/mL. For those with high risk and PSA ≤3 ng/mL and those with average risk and PSA 1–3 ng/mL, 1- to 2-year intervals are recommended. Further evaluation can be considered

for younger patients and for those who have PSA levels that are above the median for their age group, even if they do not meet the threshold of >3 ng/mL. For patients >75 years of age, repeat testing is recommended at 1- to 3-year intervals if PSA is <4 ng/mL, but only in very healthy people with little or no comorbidity. Discontinuation of screening can be considered if clinically appropriate. Clinical judgment and shared decision-making should be used to determine the testing interval within these ranges for each individual.

Age at Which to Discontinue Testing

Panelists uniformly agree that PSA testing should not be offered to individuals with a life expectancy of <10 years. Several resources exist to help clinicians estimate life expectancy, such as the Social Security Administration's Actuarial Life Table, the WHO's Life Tables, and the Memorial Sloan Kettering's Male Life Expectancy tool. However, the ideal age at which to discontinue screening for asymptomatic individuals with normal PSA levels is unknown. A balance is needed between limiting unnecessary biopsies/overdiagnosis and maximizing the detection of aggressive disease that could threaten the lives of older individuals.

Since the previously cited RCTs (ERSPC, PLCO, and Göteborg) observed benefits to testing only in participants aged ≤70 years, several Panel members favored stopping testing at age 70 years.

However, other data would suggest a benefit to screening beyond 70 years. A study of 4561 patients who underwent radical prostatectomy found that those >70 years were more likely to have higher grade and stage of disease and worse survival compared to those ≤70 years.[113] Others have published similar findings.[114] In addition, an analysis of the SEER database showed that patients who were diagnosed with prostate cancer at >70 years of age were more likely to die of their disease than those diagnosed at <70 years (21% vs. 17%).[115] A separate analysis of

the SEER database showed that patients whose prostate cancer was diagnosed at ≥75 years were more likely to have advanced disease and had a higher risk of death from prostate cancer despite greater death rates from competing causes than those diagnosed at < 75 years.[116] Another cohort study in Sweden showed similar results but also showed that patients who are older may not receive sufficient diagnostic workup and curative treatment, thus confounding the interpretation of the results.[117] Another possible issue with the interpretation of these studies is that fewer of the patients >70 years may have undergone PSA-based early detection than in the <70-year-old population, explaining the higher prevalence of advanced disease at diagnosis.

To assess the appropriate ages for discontinuing screening, the previously cited microsimulation model[111] predicted that decreasing the stopping age from 74 to 69 years would lead to a 27% relative reduction in the probability of life saved, but to an almost 50% reduction in the probability of overdiagnosis. This latter finding reflects the fact that a large proportion of individuals >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 disease in this age group that could benefit from earlier detection.

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

PSA at certain ages may predict future risk. Vickers and colleagues[106] examined the relationship between baseline PSA at age 60 years and the future risk of prostate cancer death or metastases and found that those with a PSA level below the median (<1 ng/mL) were unlikely to develop clinically significant prostate cancer (0.5% risk of metastases and 0.2% risk of prostate cancer death). Similarly, in a study of 849 individuals in the Baltimore Longitudinal Study of Aging (BLSA), no individuals aged 75 to 80 years with a PSA <3.0 ng/mL died of prostate cancer.[118] Moreover, the time to death or diagnosis of aggressive prostate cancer was longer in those with a PSA <3.0 ng/mL versus those with a PSA >3.0 ng/mL, suggesting that individuals ≥75 years with a PSA <3.0 ng/mL are unlikely to die or experience aggressive prostate cancer throughout their remaining life and most may safely discontinue screening.

In summary, many possible strategies to reduce overdiagnosis in the older population exist. Individuals ≥60 years with a PSA <1.0 ng/mL and those >75 years with a PSA <3.0 ng/mL have a very low risk of prostate cancer metastases. Continuing screening beyond age 75 years should be performed only with caution in very healthy patients with little to no comorbidity, especially if they have never undergone PSA testing or have increasing PSA levels (category 2B for continuing screening beyond age 75 years), to detect the small number of aggressive cancers that pose a significant risk if left undetected until signs or symptoms develop. Widespread testing in this population would substantially increase rates of overdetection and is not recommended. Individuals >75 years who choose to continue PSA-based prostate cancer early detection (category 2B) and who have a PSA <4 ng/mL, a normal DRE (if done), and no other indications for biopsy can undergo repeat testing at 1- to 3-year intervals (or consider discontinuing screening if clinically appropriate), but again only in very select patients. Those with a PSA ≥4 ng/mL and/or a DRE that is very suspicious for cancer should undergo further evaluation as indicated in the guidelines.

Transgender and Gender-Diverse Populations

Transgender women and other gender-diverse individuals with a prostate are a growing segment of the population who warrant special consideration. The prostate is not removed in any form of gender-affirmation surgery, and all individuals with prostates remain at risk of prostate cancer. However, rates of prostate cancer in transgender women appear to be lower than that in cisgender males.[119] However, the largest published case series on prostate cancer in transgender women to date (N = 155) showed that patients on gender-affirming hormones had more aggressive disease at diagnosis, suggesting potential delays in diagnosis of clinically significant disease.[120] Thus, clinicians should engage transgender women and gender-diverse individuals with a prostate in shared decision-making regarding age-appropriate PSA screening.

For those on gender-affirming hormones, such as estrogen, PSA values should be interpreted cautiously as existing reference ranges do not account for the castrating effects of gender-affirming hormones and are likely not appropriate for use in this population. A retrospective study found that the median PSA level was 0.02 ng/mL (interquartile range [IQR], 0–0.2; 95th percentile, 0.6 ng/mL) in 210 transgender women with a median age of 60 years who were on estrogen for at least 6 consecutive months and had no known prostate cancer.[119] The study reported that similarly aged cisgender men without prostate cancer have a median PSA of 1 ng/mL in other studies.

Future dedicated studies are needed to define optimal screening practices and, specifically, to determine proper thresholds to define elevated PSA levels in transgender and gender-diverse individuals with a prostate undergoing gender-affirming care. In the meantime, clinicians should take the far lower PSA values into account when interpreting PSA values and pay special attention to rising PSA levels in this population. Further

evaluation may be warranted even if values are within existing reference ranges.

Screening in Populations With Elevated Risk

Individuals with a concerning family or personal history, Black/African American individuals, and those with certain germline mutations have a higher risk of developing prostate cancer, as discussed in further detail below.[121-127] In addition, hormone disrupters such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the carcinogenic chemical compound found in the herbicide Agent Orange, may also be linked to the development of prostate cancer.[128,129] Patients with exposure to Agent Orange (eg, many Vietnam War veterans) should be informed that exposure to this chemical may be associated with an increased risk of high-grade prostate cancer.

Family History

Having a first-degree relative with prostate cancer diagnosed before the age of 60 increases the likelihood of a prostate cancer diagnosis by 2.1- to 2.5-fold.[123,124] Furthermore, in individuals who have a sibling with aggressive prostate cancer, the OR for aggressive prostate cancer is 1.21 (95% CI, 1.04–1.39).[130] A population-based study in Sweden found that the risk for the development of prostate cancer increased with the number of affected relatives.[131] Data, however, suggest that prostate cancer in individuals with a family history of prostate cancer is not more likely to be aggressive, and cancer-specific outcomes are similar between those with and without a family history.[126,132,133]

Prostate cancer risk is also elevated in patients with a family history of breast cancer.[134,135] The Panel lists cancer types that should be considered during the family and personal cancer history risk assessment in the guidelines above. Patients with a suspicious family history should undergo genetic testing.

It is important to note that those with a family history of prostate cancer are more likely to undergo screening and biopsy than those without a family history. Therefore, the role of family history as a risk factor for prostate cancer may be overestimated.[136] Welch and Brawley refer to this phenomenon as "self-fulfilling risk factors" in cancers that are "scrutiny-dependent."[137]

Genetic Syndromes

Data indicate that patients with prostate cancer may have germline mutations in 1 of 16 DNA repair genes: *BRCA2* (5%), *ATM* (2%), *CHEK2* (2%), *BRCA1* (1%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*.[138] Individuals with these inherited mutations may have an increased risk for prostate cancer. Several inherited syndromes are discussed below. In addition, individuals who carry the rare 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.[139-141] *HOXB13* mutations are more frequent among families of Scandinavian heritage. *HOXB13* X285K is another rare variant, found in individuals of West African ancestry, which may also be associated with an increased risk of prostate cancer.[142]

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

In addition, patients who meet hereditary risk assessment criteria established in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal,

Endometrial, and Gastric (available at www.NCCN.org) should be referred for genetic counseling/testing as appropriate.[143] For prostate cancer susceptibility genes and cancer risk management based on genetic testing results, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (GENE-A and BRCA-A; available at www.NCCN.org).

Information regarding the status of high-risk germline mutations should be used as part of the discussion about prostate cancer early detection; patients may not be aware of the increased risk for prostate cancer associated with such mutations.

Lynch Syndrome

Lynch syndrome is a hereditary cancer syndrome caused by pathogenic germline mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) or in *EPCAM*.[144] Lynch syndrome is predominantly associated with colorectal and endometrial cancers, but individuals with Lynch syndrome also have a 2- to 5.8-fold increase in risk for prostate cancer.[145-150] Age of onset and aggressiveness of prostate cancer in these individuals do not generally appear to be different than in sporadic cases.[146,149] Interestingly, a study of 524 families with pathogenic germline *PALB2* alterations found no evidence for an increased risk of prostate cancer.[151]

The ongoing international IMPACT study prospectively enrolled participants aged 40 to 69 years with germline mutations in *MLH1*, *MSH2*, or *MSH6* (n = 644) and age-matched, related controls without the germline mutations (n = 184).[144] An additional 134 non-carriers from the *BRCA1/2* cohort of the IMPACT study were randomly selected to be included in the control group. All participants are required to have annual PSA testing for a minimum of 5 years. After the first round of PSA screening, the incidence of prostate cancer was 4.3% among *MSH2* carriers (13 of 305; 95% CI, 2.3–7.2), 3.0% among *MSH6* carriers (4 of 135; 95% CI, 0.8–7.4),

and 0.5% among *MSH2* non-carrier controls (1 of 210; 95% CI, 0–2.6). None of the *MLH1* carriers or the other non-carrier control participants were diagnosed with prostate cancer.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is caused by a pathogenic germline variant in *TP53*. Individuals with LFS have an increased risk of many primary cancers, most commonly breast cancer, osteosarcomas, adrenocortical carcinomas, central nervous system (CNS) tumors, and soft tissue sarcomas.[152] It is also associated with an approximately 9-fold increased risk of prostate cancer.[153] Data also suggest that individuals with germline *TP53* mutations are more likely to develop aggressive prostate cancer.[153]

Hereditary Breast and Ovarian Cancer Syndrome

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.[154,155] These mutations have been associated with an increased risk for prostate cancer in numerous reports.[156-165] 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.[157,159,160,165-168] Furthermore, prostate cancer in those with germline *BRCA* mutations appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in patients who are non-carriers.[169-174]

Interim results of the IMPACT study, which prospectively enrolled participants aged 40 to 69 years with germline *BRCA1/2* mutations (919 *BRCA1* carriers; 902 *BRCA2* carriers) and a control group with wild-type *BRCA1/2* who are related to mutation carriers (709 *BRCA1* non-carriers; 497 *BRCA2* non-carriers), were reported in 2019.[175] All participants underwent annual PSA testing four times. Whereas no differences were

seen between *BRCA1* carriers and non-carriers, the *BRCA2* carriers had a higher cancer incidence rate (19.4 per 1000 person years vs. 12.0; *P* = .03); were diagnosed at a younger age (61 vs. 64 years; *P* = .04); and were more likely to have clinically significant disease (77% vs. 40%; *P* = .01) than *BRCA2* non-carriers. One limitation of the study is that the biopsy completion rate was higher in *BRCA2* carriers compared with non-carriers (73% vs. 60%). Further follow-up is required to assess the clinical utility of this early detection strategy.

African Ancestry

Black individuals and those with African ancestry have a 60% higher incidence of prostate cancer, earlier age at diagnosis, and a 36% to 39% increase in prostate cancer mortality compared with white individuals.[125,176,177] Data also show that Black individuals are more likely to have aggressive prostate cancer and to be diagnosed with more advanced disease.[178-181] Modeling studies indicate that Black individuals likely have a higher incidence of preclinical disease and an increased risk of metastatic progression than white individuals.[182] A logistic regression analysis of SEER data from 2004 to 2011 determined that Black individuals also had a decreased likelihood of receiving treatment even when diagnosed with high-risk disease. [183] In fact, data showed an inverse relationship between disease severity and probability of receiving treatment in Black individuals.

Furthermore, autopsy data indicate that prostate cancer may undergo transformation to aggressive disease earlier in Black/African American individuals than in white American individuals.[184] In addition, data suggest that Black/African American individuals have an earlier onset of prostate cancer. An analysis of SEER data from 2010 found that non-Hispanic African American individuals are diagnosed with prostate cancer an adjusted average of 1.2 years earlier than non-Hispanic white American individuals,[185] whereas an older SEER analysis found that African

American individuals were diagnosed at an average of 3 years younger than white American individuals.[186] A retrospective, population-based cohort study in the United Kingdom found that Black individuals were diagnosed an adjusted average of 5.1 years earlier than white individuals.[187] Another study estimated that African American people have an almost 2-fold higher risk of being diagnosed with prostate cancer before the age of 45 than white American people.[186]

The main drivers for these racial inequities are likely lower rates of prostate cancer screening, diagnostic procedures, and overall access to health care; treatment disparities; inadequate health insurance coverage; and other factors related to social determinants of health (eg, environmental exposures; patient and physician behaviors; delays in diagnosis).[181,188-193] Further evidence supports the likelihood that such inequities are not related to race itself or differences in the frequency of tumor-acquired genomic variants.[194] In fact, data show that Black patients who receive equitable prostate cancer treatment have similar outcomes to white patients.[195]

Despite these inequities, prostate cancer screening has been predominantly studied in white individuals. In the PLCO trial, non-Hispanic Black participants only made up approximately 4.4% of the trial population, and 6.9% had a positive family history, but no subset analyses were performed.[95] In the ERSPC trial, no information on ancestry or family history was reported.[72]

Some data have informed how different prostate cancer early detection protocols could be used to decrease these racial inequities. For example, a study of 41,250 individuals 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 individuals than in white American individuals (1.9 vs. 2.5 ng/mL).[196] The prospective Southern Community Cohort Study found that Black

individuals with PSA above the 90th percentile at ages 40 to 64 years had a greatly elevated risk of aggressive prostate cancer compared with the risk of those whose PSA levels were below the median.[108] Another analysis that estimated cases of overdiagnoses and overtreatment and calculated numbers needed to diagnose and numbers needed to treat to prevent one prostate cancer death in individuals of all races and Black individuals, found a more favorable harm-benefit ratio of PSA screening in Black individuals versus all races combined.[197] In addition, a modeling study looked at the effects of different PSA testing intervals in Black individuals and found that a shorter interval could reduce mortality without increasing the risk of overdiagnosis in this population.[112]

Based on these data, the Panel recommends that Black/African American individuals consider beginning shared decision-making about PSA screening at age 40 years and that they consider screening at annual intervals rather than every other year.

Recommendations for Early Detection in Populations with Elevated Risk

In conclusion, Black/African American individuals, individuals with a suspicious family or personal cancer history, and those with a known genetic predisposition represent groups at high risk for the development of prostate cancer. The Panel acknowledges that current data are insufficient to definitively inform the best strategy for prostate cancer early detection in these populations, but they recommend the following based on the data above and Panel consensus:

- It is reasonable for individuals with a suspicious family cancer history or known germline mutation that increases the risk for prostate cancer (as defined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate; available at www.NCCN.org) to begin shared decision-making about PSA screening at age 40 years.

- It is reasonable for Black/African American individuals to consider beginning shared decision-making about PSA screening at age 40 and to consider screening at annual rather than less frequent screening intervals. However, no current evidence shows that testing individuals of African descent at an earlier age will result in decreased morbidity and mortality compared to testing at age 45, and earlier screening may increase overdiagnosis.

Further Evaluation and Indications for Biopsy

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

The Panel does not believe that DRE alone should be an absolute indication for biopsy in individuals with low PSA. The PPV of DRE in those with low PSA is poor (see *DRE*, above).[63,198] However, a DRE that is very suspicious for cancer, independent of PSA, could be an indication of high-grade cancer in individuals with normal PSA values, and therefore biopsy can be considered. Clinical judgment should be used.

Pre-Biopsy Workup

The Panel recommends that any individual with a PSA >3 ng/mL undergo workup for benign disease, a repeat PSA, and a DRE (if not performed during initial risk assessment) to inform decisions about whether to proceed with image-guided biopsy or additional testing with other

biomarkers and/or multiparametric MRI (mpMRI). The Panel strongly recommends that mpMRI (category 1) should precede biopsy, if available. Biomarkers that improve the specificity of screening should be considered before biopsy. The roles of imaging and biomarker testing to inform biopsy decisions are discussed in detail below. The predictive value of biomarkers has not been correlated consistently with that of mpMRI. Therefore, it is not known with certainty how such tests could be applied in optimal combination.

An abnormal DRE in this setting of elevated PSA has a high predictive value,[70] and the Panel strongly recommends biopsy in these individuals.

If there is low suspicion for clinically significant cancer, individuals should be followed up in 6 to 12 months with PSA and DRE. Patients for whom there is a high suspicion of clinically significant prostate cancer 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.[68,199-205] These online tools combine clinical variables—including but not limited to age, family history, ancestry, DRE, and PSA—to estimate both the risk for biopsy-detectable prostate cancer and the risk for biopsy-detectable high-grade prostate cancer. Such information potentially allows for more informed decision-making.[206] 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; however, they can be considered when deciding

whether a biopsy can be avoided in an individual with a negative mpMRI result.

Magnetic Resonance Imaging

Considerable interest exists in using mpMRI both pre-biopsy to select patients for biopsy and during biopsy to guide needle placement.[207-214] The goals of using mpMRI in these settings include reducing the number of individuals 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.

MRI has generally been shown to have superior sensitivity for clinically significant prostate cancer when compared to image-guided biopsy. In the multicenter, paired-cohort PROMIS study, 576 participants with no prior biopsy and elevated PSA <15 ng/mL underwent mpMRI followed by transrectal ultrasound (TRUS) biopsy and perineal template mapping biopsy.[215] Clinically significant cancer (Grade Group ≥3 or a maximum cancer core length ≥6 mm by template mapping biopsy) was found in 40% of patients. In detecting clinically significant prostate cancer (some may question the cut point of ≥6 mm used), MRI was more sensitive (93%; 95% CI, 88%–96%) than TRUS biopsy (48%; 95% CI, 42%–55%; $P <$ .0001), but less specific (41%; 95% CI, 36%–46% for MRI vs. 96%; 94%–98% for TRUS biopsy; $P <$ .0001). If a normal MRI had been used to screen individuals for biopsy, 27% would have avoided biopsy. It is important to note that patients in this study did not undergo MRI-targeted biopsy, so the study does not provide direct evidence about the performance of MRI-guided biopsy.

An approach utilizing MRI prior to biopsy followed by MRI-guided biopsy, was directly compared to conventional TRUS biopsy in the PRECISION trial.[216] PRECISION was a randomized, noninferiority trial conducted in 25 centers across 11 countries. A total of 500 participants were randomized to either MRI (with or without targeted biopsy) or a 10- to 12-core TRUS biopsy. In the MRI arm, 28% avoided biopsy based on a normal MRI (Prostate Imaging Reporting and Data System [PI-RADS] <3). Clinically significant prostate cancer was detected in 38% of patients in the MRI group and in 26% in the standard biopsy group. Thirteen percent fewer participants in the MRI group received a diagnosis of low-risk disease. Because PRECISION was conducted primarily in Europe at centers of excellence in prostate MRI, the generalizability of some of its findings remain unproven. The finding that MRI before biopsy reduces negative biopsies and detection of indolent disease has been substantiated in numerous studies in both the initial and repeat biopsy settings.[217-221]

MRI-FIRST was a prospective, multicenter, paired diagnostic study conducted at 16 centers in France.[222] Each of 251 participants underwent pre-biopsy MRI, systematic biopsy, and targeted biopsy (if MRI was abnormal). Fifty-three (21%) had a normal MRI (Likert 1–2). Of these, five (11%) had clinically significant prostate cancer on systematic biopsy. Overall, clinically significant cancer (Grade Group ≥2) was found in 29.9% of patients (95% CI, 24.3–36.0) on systematic biopsy, 32.3% (95% CI, 26.5–38.4) on targeted biopsy, and 37% using combined targeted and systematic biopsy. There was no significant difference between targeted and systematic biopsy (P = .38). Clinically significant prostate cancer would have been missed in 5.2% of patients had systematic biopsy been skipped and in 7.6% had targeted biopsy been skipped. Thus, MRI-FIRST demonstrates that adding MRI-targeted biopsy for those without prior biopsy improves the yield of clinically significant prostate cancer, but that maximizing detection of clinically significant prostate cancer does require the combination of targeted and systematic biopsy. The study protocol allowed for different methods of targeted biopsy (cognitive and fusion), and MRIs were read locally. Still, generalizability questions remain because all study centers had experience with prostate MRI and targeted

biopsy, two centers enrolled 36% of all patients, and interobserver agreement in MRI interpretation was not addressed.

A similar prospective, multicenter comparative effectiveness study (the 4M study) included 626 patients who were biopsy-naïve at four centers in the Netherlands.[223] All patients underwent pre-biopsy MRI followed by systematic biopsy. Those with abnormal MRI also underwent in-bore MRI-guided biopsy. All MRIs were centrally reviewed by two highly experienced radiologists who were experts in prostate MRI. Overall, 49% of MRIs were read as normal (PI-RADS 1–2) and only 6% as indeterminate (PI-RADS 3). Clinically significant cancer (Grade Group ≥2) was detected in 30% of participants using the combined approach, in 25% using the MRI-targeted approach, and in 23% using a systematic approach. No difference in clinically significant prostate cancer detection was seen between targeted and systematic biopsy (difference, 2%; 95% CI, -1 to 5). Similar to PRECISION and MRI-FIRST, detection of insignificant cancer was lower using the targeted approach (difference, 11%; 95% CI, 7–14). Not biopsying those with PI-RADS 1–2 MRI missed only 4% of those with clinically significant prostate cancer detected on systematic biopsy. Among the 317 individuals with an abnormal MRI, 21 (7%) had cancer detected only on systematic biopsy. This study is remarkable for the high proportion of individuals (49%) who could have avoided biopsy based on a normal MRI while still maintaining an equivalent detection of clinically significant prostate cancer when compared to systematic biopsy for all individuals. Like MRI-FIRST and multiple retrospective studies, this study also shows that a relatively small proportion of clinically significant prostate cancer would be missed by omitting systematic biopsy. The authors acknowledge that this study represents the best-case scenario where MRI is performed and interpreted by experts and targeted biopsy is performed by experts. The results may not be widely generalizable without extensive training of radiologists and urologists, but the potential for the MRI-targeted approach is relatively high for achieving the goals of reducing biopsies, maximizing

detection of clinically significant prostate cancer, and reducing overdetection of indolent cancer.

Another similar study, STHLM3-MRI, included 1532 individuals in Sweden with PSA levels ≥3 ng/mL who were randomly assigned 2:3 to undergo standard biopsy (n = 603) or to an experimental group that had an MRI evaluation with both targeted and standard biopsy if the MRI suggested the presence of prostate cancer.[224] As in the previously described trials, the experimental approach led to the diagnosis of fewer clinically insignificant cancers. It was also noninferior to standard biopsy for detecting clinically significant cancer.

In the Trio study, 2103 patients with prostate lesions visible by MRI underwent both MRI-targeted and systematic biopsy.[225] The primary outcome measure was cancer detection according to Grade Group. The rate of detection of Grade Group 1 cancers was significantly lower by MRI-targeted biopsy than by systematic biopsy, whereas the rate of detection of Grade Group ≥3 cancer was significantly higher with MRI-targeted biopsy ($P < .01$ for all comparisons). Of the 404 participants who underwent subsequent radical prostatectomy, upgrading to Grade Group ≥3 cancer occurred in 16.8% based on systematic biopsy, 8.7% based on MRI-targeted biopsy, and 3.5% based on the combination. The combined approach also resulted in 59 additional cancer diagnoses of Grade Group ≥3 than would have been found by use of either method alone.

The Canadian multicenter, prospective, randomized PRECISE clinical trial included 453 patients who were biopsy-naïve with a clinical suspicion of prostate cancer and PSA ≤20 ng/mL.[226] Participants were randomized to undergo MRI followed by targeted biopsy only if the PI-RADS score was ≥3 (MRI-TB) or systematic TRUS biopsy. The primary outcome measure, the proportion of participants with a diagnosis of Grade Group 2 or greater cancer, was similar in the two groups (35% vs. 30%, respectively; absolute difference, 5%; 97.5% 1-sided CI, -3.4% to infinity; noninferiority margin, -

5%). Thus, the MRI-TB approach was noninferior to the systematic TRUS biopsy approach. Importantly, 37% of participants in the MRI-TB group had a negative MRI and avoided biopsy, adverse events were less common in the MRI-TB group, and the detection of Grade Group 1 cancer was lower in the MRI-TB group (22% vs. 10%; risk difference, -11.6%; 95% CI, -18.2% to -4.9%).

The large, population-based, randomized GÖTEBORG-2 trial included >37,000 individuals aged 50 to 60 years who had regular PSA testing.[227] Participants with PSA levels ≥3 ng/mL received a prostate MRI and were randomized 2:1 to receive MRI-targeted biopsy only (experimental group) or targeted biopsy and systematic biopsy (reference group). All of the 5994 patients in the reference group were biopsied, whereas 262 of 11,986 participants (of 268 with positive MRI) underwent targeted biopsy in the experimental group. Results indicated that 66 individuals in the experimental group (0.6%) and 72 in the reference group (1.2%) received a diagnosis of clinically insignificant prostate cancer (95% CI, −1.0 to −0.4; RR, 0.46; 95% CI, 0.33–0.64; $P < .001$). Clinically significant prostate cancer was diagnosed in 110 individuals in the experimental group (0.9%) and 68 individuals in the reference group (1.1%; RR, 0.81; 95% CI, 0.60–1.10). Ten clinically significant prostate cancers, all of which were intermediate risk, were detected by systematic biopsy (0.2%). After additional rounds of screening and a median follow-up of 3.9 years, a recent analysis of the GÖTEBORG-2 trial found that more high-risk cancers were detected in the reference group (23) compared to the experimental (15), with an RR of 0.65 (95% CI, 0.34–1.24).[228] Data from this study thus show an approximately 50% decreased risk of detecting clinically insignificant prostate cancers when systematic biopsies are omitted, with diagnoses of intermediate-risk and high-risk cancers remaining about the same. However, the low biopsy rate in the experimental group makes it impossible to know the true numbers of missed cancers in that group, and the Panel continues to recommend the use of both systematic and targeted biopsies.

Many other studies support the notion that incorporating MRI-targeted biopsies into initial biopsies can improve the detection of clinically significant disease and also note that fewer significant upgrades are seen at radical prostatectomy in those who underwent initial biopsy using MRI targeting.[209,229-233] However, evidence from other studies is mixed as to whether MRI-guided biopsy improves clinically significant prostate cancer detection in individuals without a prior biopsy.[211,222,234] For example, a single-center trial randomized 130 individuals who were biopsy-naïve to a control group that received TRUS-guided random biopsy alone or to a group that received pre-biopsy mpMRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion-targeted biopsy.[211] 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 patients who were biopsy-naïve with suspected prostate cancer were assigned to a pre-biopsy mpMRI group or to a standard biopsy group.[234] Participants in the mpMRI group had targeted fusion biopsies if suspicious lesions were seen. Otherwise, they received standard biopsies. More clinically significant prostate cancers were detected in the mpMRI arm (43.9% vs. 18.1%; $P < .001$).

Similar to the studies above, multiple retrospective studies have shown that adding MRI-targeted biopsy to systematic biopsy increases the yield of clinically significant prostate cancer over systematic biopsy alone. A 2019 Cochrane systematic review identified 18 cross-sectional studies that compared template-guided biopsy with MRI only, MRI-targeted biopsy, MRI with or without MRI-targeted biopsy, and/or systematic biopsy for the detection of Grade Group ≥2 prostate cancer.[235] The authors concluded that MRI with or without MRI-targeted biopsy detects a greater number of significant cancer while detecting fewer insignificant cancers compared

with systematic biopsy. Another systematic review suggests that the approach of MRI first in individuals who are biopsy-naïve may improve detection of clinically significant cancer, reduce the number of biopsy cores per procedure, reduce adverse effects, and potentially reduce unnecessary biopsies.[236]

In summary, the data suggest that a significant proportion of people who are biopsy-naïve with elevated PSA can avoid biopsy based on a PI-RADS ≤2 result on mpMRI (21%–49%), but some of these people have clinically significant disease that would be missed (2%–14% of the study populations).[216,222,223,226,237-239] It is important to note that a similar or possibly higher proportion of clinically significant disease is missed with a traditional approach of proceeding to a systematic biopsy without a mpMRI, with higher detection of indolent disease.[222,240]

The Panel also notes that the vast majority of published evidence using MRI for prostate cancer diagnosis comes from high-volume centers of excellence. The generalizability of these findings is not yet clear. In light of evidence showing considerable interobserver variability in the interpretation of prostate MRI, the Panel emphasizes the need for high-quality mpMRI and radiologic expertise for optimal reading of scans.[241-243] The PI-RADS from the American College of Radiology gives recommendations for high-quality MRI in prostate cancer care, including recommendations related to the use of MRI to direct targeted biopsies (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Reporting-and-Data-Systems/PI-RADS).

At this time, the Panel strongly recommends that an mpMRI (category 1) evaluation (if available) be performed before proceeding to an image-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, even with the best equipment and readers due to the negative predictive value (NPV) for clinically significant prostate cancer

(around 86%–98%).[216,222,223,226,237,238] Therefore, proceeding to image-guided biopsy following a negative MRI should still be considered, particularly in situations where the patient is considered to be at high risk for cancer based on PSA density or other biomarkers.[218,244-246]

The Panel also recommends that image-guided biopsy techniques should be used routinely (see *Targeted Biopsy Techniques*, below). Radiologic expertise and the use of high-quality mpMRI hardware is essential for optimal interpretation of scans. Although some advocate for excluding systematic biopsy in those undergoing MRI targeting (due to concerns that it may increase the risk of overdiagnosis), most advocate for a combined approach (preferred) as some high-grade cancers are uniquely detected using the systematic approach and systematic biopsies are needed for risk stratification if cancer is found.

In individuals with at least one negative biopsy, the Panel believes that high-quality mpMRI may help identify regions of cancer missed on prior biopsies; it should therefore be considered in this setting if not done previously (also see *Repeat Biopsies*, below).[247]

Biparametric MRI

As discussed above, the use of mpMRI is a preferred (category 1) diagnostic tool for accurately detecting and localizing prostate cancer. However, due to various circumstances, mpMRI, which includes dynamic contrast-enhanced (DCE) imaging, is not always available to individuals who require MRI for prostate cancer identification and staging. Biparametric MRI (bp-MRI), which does not include DCE imaging, offers a diagnostic alternative to patients and clinicians that allows measurement of both the prostate and lesion volume. The use of bp-MRI can shorten scan times, meet increasing demand for diagnostic workups, lower costs, increase patient comfort, and reduce the risk of allergic reactions to imaging agents such as gadolinium while remaining diagnostically accurate for high-grade prostate cancer detection. Several diagnostic

values of bp-MRI and mpMRI were equal, including sensitivity of 95% (95% CI, 91–97), specificity of 69% (95% CI, 64–73), NPV of 97% (95% CI, 94–98), and PPV of 57% (95% CI, 51–62).[248] A further study reached similar conclusions when analyzing data from the PROMIS trial.[249] The authors reported values of sensitivity (94% and 95%), specificity (37% and 38%), PPV (51% and 51%), and NPV (90% and 91%) for MRI without and with DCE imaging ($P > .05$) in cases of significant prostate cancer. It is noted that among expert diagnostic readers, there is some uncertainty that may arise without dynamic contrast.[250]

Biomarker Testing

When the first recommendations for early detection programs for prostate cancer were made, serum PSA 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 more precisely estimate the risk 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 which patients should consider biopsies, decreasing unnecessary biopsies, and increasing the specificity of cancer detection, without missing a substantial number of higher-grade (Grade group ≥2) cancers. These tests may be especially useful in individuals with PSA levels between 3 and 10 ng/mL. Most often, these tests have been used in patients who have had one negative biopsy to determine if repeat biopsy is an appropriate consideration.

The Panel recommends consideration of biomarker tests that meet criteria of both validity and clinical utility as outlined in the guidelines above. The extent of validation of these tests varies across diverse populations (see

below). Results of biomarker assays can be complex and should be interpreted with caution. Referral to a specialist should be considered, and risk calculators are also a consideration in these same patients.

Importantly, mpMRI is recommended if available, but it is not yet known with certainty how biomarker tests can be applied in optimal combination with MRI. It also remains unclear how to interpret results of multiple tests in individual patients, especially when results are contradictory. However, several studies suggest that upfront biomarker testing with conditional MRI may be an efficient and effective way to assess those with a persistently elevated PSA.[251-254]

Head-to-head comparisons have been performed for some of these tests, used independently or in combinations in the initial or repeat biopsy settings, but sample sizes were often small and results varied.[255-267] Therefore, the Panel believes that no biomarker test can be recommended over any other at this time.

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

%fPSA

Unbound or free PSA (fPSA), expressed as a ratio of tPSA, is a clinically useful molecular form of PSA, with the potential to improve early detection, staging, and monitoring of prostate cancer. Several molecular forms of PSA are known to circulate in the blood. In most individuals, the majority (60%–90%) of circulating PSA is covalently bound to endogenous protease inhibitors. Most immunoreactive PSA is bound to the protease inhibitor alpha-1-antichymotrypsin. Other immunoreactive PSA-protease inhibitor complexes, such as alpha-1-antitrypsin and protease C inhibitor, exist at such low serum concentrations that their clinical significance has

not been determined. In addition, a large proportion of PSA is complexed with alpha-2-macroglobulin (AMG). Unfortunately, this PSA-AMG complex cannot be measured by conventional assays because of the shielding (or "caging") of PSA antigenic epitopes by AMG.

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

The U.S. Food and Drug Administration (FDA) approved the use of %fPSA for the early detection of prostate cancer in individuals aged ≥50 years with a non-suspicious DRE and PSA levels between 4 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.[268]

Since its approval by the FDA, testing for %fPSA has gained widespread clinical acceptance in the United States, and it is included in the guidelines as an option before initial biopsy and for those with a prior negative biopsy.

PSA Density

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

PSA density is a means of discriminating prostate cancer from BPH: the lower the PSA density, the greater the probability of BPH.[269,270] Thus, PSA density potentially identifies individuals who do not have prostate cancer but have high PSA secondary to large-volume prostates. A PSA density

cutoff of 0.15 ng/mL/g was recommended in earlier studies, which spared as many as 50% of individuals from unnecessary biopsies. However, some subsequent studies have reported that the 0.15 ng/mL/g cutoff has insufficient sensitivity.[271]

PSA density has also been shown to correlate with prostate cancer presence and aggressiveness, and may predict adverse pathology and biochemical progression after treatment.[272,273] Therefore, the Panel believes that PSA density should be considered when deciding whether to proceed to a biopsy in an individual with a negative mpMRI result or for any patient who is biopsy-naïve with an elevated PSA.

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.[274-277] For example, in a prospective multicenter clinical study of 466 individuals with at least one prior negative prostate biopsy, a PCA3 score cutoff of 25 showed a sensitivity of 78%, specificity of 57%, NPV of 90%, and PPV of 34%.[274] Participants with a score of ≥25 were 4.6 times more likely to have a positive repeat biopsy than those with a score <25.

Results were reported from an National Cancer Institute (NCI) Early Detection Research Network (EDRN) validation study of the PCA3 urinary assay in 859 individuals scheduled for a diagnostic prostate biopsy in 11 centers.[278] The primary outcomes were reported at a PPV of 80% (95% CI, 72%–86%) in the initial biopsy setting and an NPV of 88% (95% CI, 81%–93%) in the repeat biopsy setting. Based on the data, use of PCA3 in the repeat biopsy setting would reduce the number of biopsies by almost half, and 3% of those with a low PCA3 score would have high-grade prostate cancer that would be missed. In contrast, the risk of high-grade

disease in those without prior biopsy with a low PCA3 is 13%. Thus, the Panel believes that this test is not appropriate to use in the initial biopsy setting.

The FDA has approved the PCA3 assay to help decide, along with other factors, whether a repeat biopsy in individuals aged ≥50 years with one or more previous negative prostate biopsies is necessary. This assay is recommended for those with a previous negative biopsy in order to avoid repeat biopsy by the Molecular Diagnostic Services Program (MolDX) and is therefore covered by the Centers for Medicare & Medicaid Services (CMS) in this setting. The Panel also includes PCA3 as an option in the post-biopsy setting.

PHI

The Prostate Health Index (PHI) is a combination of the tPSA, fPSA, and proPSA tests.[279-281] 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.[282] In addition, the PHI correlated with cancer grade and had an AUC of 0.72 for discrimination of high-grade (Grade Group ≥2) cancer from low-grade cancer or negative biopsy. Another prospective cohort study calculated an AUC of 0.815 for the detection of high-grade (Grade Group ≥2) prostate cancer.[283] 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.[252,284-286]

The PHI was approved by the FDA in 2012 for use in those with serum PSA values between 4 and 10 ng/mL. A clinical utility study conducted at four large urology group practices showed that use of PHI was in fact associated with a decrease in biopsy procedures performed when compared to historical controls from the same physicians (36.4% vs. 60.3%; $P < .0001$).[287] Patients in the study had normal DRE and PSA values ranging from 4 to 10 ng/mL. Physician survey results showed that PHI results impacted biopsy decisions for 73% of patients. However, the authors of this study did not report the numbers of high-grade cancers missed, and some have estimated that it may be as high as 30%.[288]

PHI is included as an option in the guidelines in both the pre- and post-biopsy settings.

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.[289,290] This test reports the percent likelihood of finding high-grade (Grade Group ≥2) cancer on biopsy. A prospective multi-institutional U.S. trial of 1012 patients showed that 4Kscore results have a high discrimination value (AUC, 0.82).[291] In this study, using a threshold for biopsy of ≥15% risk allowed for 591 biopsies to be avoided (58%), while 183 high-grade tumors were detected and 48 high-grade tumors (4.7% of the 1012 participants) were missed. When 4Kscore was examined in 6129 participants in another prospective study, the AUC was also 0.82 (95% CI, 0.80–0.84).[292] Using a 6% risk of high-grade cancer as a cutoff, 428 of 1000 individuals could avoid biopsy, with 119 of 133 high-grade cancers detected and 14 of 133 missed. A multicenter clinical utility study found a 65% reduction in prostate biopsies with use of the 4Kscore test.[293] In addition, a correlation between 4Kscore risk category and Gleason score was seen ($P < .01$). A meta-analysis that included 12 clinical validation studies (11,134 patients) led to a calculated pooled AUC for discrimination of Grade Group ≥2 prostate cancer of 0.81 (fixed effects 95% CI, 0.80–0.83).[294]

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, patients and their urologists should discuss the results to decide whether to proceed with a biopsy.

ConfirmMDx

ConfirmMDx is a tissue-based, multiplex epigenetic assay that aims to improve the stratification of individuals being considered for repeat prostate biopsy. Hypermethylation of the promoter regions of *GSTP1, APC,* and *RASSF1* is assessed in core biopsy tissue samples. The test, performed in one Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, is not FDA approved.

The European MATLOC study blindly tested this assay in archived tissue from 498 patients with negative biopsies who had repeat biopsies within 30 months.[295] The NPV was 90% (95% CI, 87%–93%). In a multivariate analysis, ConfirmMDx was predictive of patient outcomes (OR, 3.17; 95% CI, 1.81–5.53). A similar validation study was performed in the United States using archived tissue from 350 patients with negative biopsies who had repeat biopsies within 24 months.[296] The NPV was 88% (95% CI, 85%–91%), and the test was again found to be predictive of outcomes on multivariate analysis (OR, 2.69; 95% CI, 1.60–4.51).

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

ExoDx Prostate (IntelliScore)

ExoDx Prostate (IntelliScore), also called EPI, evaluates a urine-based 3-gene exosome expression assay utilizing *PCA3* and *ERG* RNA from urine, normalized to *SPDEF*. The background for these markers is supported by a number of studies, but the application to exosome detection is unique.[297] This gene panel proposes to discriminate Grade Group ≥2 prostate cancer from Grade Group 1 and benign disease at initial biopsy. The population for which use of the assay was intended includes patients >50 years with no prior biopsy and a PSA value between 2 and 10 ng/mL. In a 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.[298] Applying a cutoff value from the training cohort to serve as a threshold for biopsy in the validation cohort decreased the need for biopsy by 27% (138 of 519) while missing 8% (12 of 148) of Grade Group ≥2 cancers. The investigators propose this assay as a secondary or reflex test for risk stratification in conjunction with PSA screening. In the McKiernan study, the algorithm was validated in a test set of 255 patients and then validated in the extended screening validation cohort of 519 patients. The majority of exclusions were for urine volume >49 mL, assay failure, and application outside the intended use population.

A second independent validation study was a 2-phase adaptive clinical utility study that included 503 patients who were biopsy-naïve with PSA levels between 2 and 10 ng/mL and compared EPI and biopsy results.[299] In the first phase of this study, the AUC was 0.70 for predicting Grade Group ≥2 cancer by EPI. Using the validated cut point of 15.6, the test has an NPV of 89%, reducing total biopsies by 20% and missing 7% of Grade Group ≥2 cancer. The second phase of this trial will be reported in the future.

In a clinical utility study, 1094 patients (with 72 urologists from 24 urology practices) were randomized to receive EPI results before biopsy or not. The EPI test results influenced the decision to proceed to biopsy in many instances, and 30% more high-grade prostate cancers were diagnosed than in the control arm.[300] The authors estimate that 49% fewer high-grade prostate cancers were missed in the EPI arm than in the control group.

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

SelectMDx

SelectMDx is a gene expression assay performed on post-DRE urine that measures *DLX1* and *HOXC6* expression against *KLK3* as internal reference. *DLX1* and *HOXC6* have been associated with prostate cancer aggressiveness.[301,302] As with other assays, SelectMDx is designed to improve the identification of individuals with clinically significant prostate cancer prior to biopsy, thereby reducing the number of unnecessary biopsies.

The assay was developed on an initial training set of 519 patients from two prospective multicenter studies and was then validated in a separate set of 386 patients from these trials.[303] Using the expression of *DLX1* and *HOXC6* alone resulted in an AUC of 0.76, a sensitivity of 91%, a specificity of 36%, an NPV of 94%, and a PPV of 27% for the prediction of Grade Group ≥2 prostate cancer. When the gene expression was combined with PSA levels, PSA density, 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.[304] 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.

A multicenter study used pre-biopsy urine samples from 1955 individuals to validate the assay with a training cohort and a validation cohort.[305] The AUC was 0.85, the sensitivity was 93%, the specificity was 47%, and the NPV was 95% for detection of Grade Group >2 prostate cancer in the 916-patient validation cohort. When only those with PSA levels <10 ng/mL were included, the values were 0.82, 89%, 53%, and 95%, respectively.

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

IsoPSA

IsoPSA is a blood-based assay that uses an aqueous 2-phase system to partition and detect PSA isoforms in blood.[306] In a prospective, multicenter validation study, IsoPSA was assessed as a diagnostic biomarker test in 888 patients scheduled for prostate biopsy.[307] IsoPSA demonstrated an AUC of 0.783 (95% CI, 0.752–0.814) for high-grade prostate cancer (Grade Group ≥2), with a sensitivity of 90.2% (95% CI, 86.4–93.0), specificity of 45.5% (95% CI, 41.4–49.6), PPV of 47.7% (95% CI, 45.7–49.8), and NPV of 89.3 (95% CI, 85.6–92.2).

In a real-world clinical utility study (n = 900), 38 clinicians practicing across a range of academic and community settings altered their pre-test recommendations for or against biopsy and/or MRI for 66% of patients after using the IsoPSA test in clinical practice, resulting in a net decrease in biopsy recommendations of 55%.[308]

The Panel believes that IsoPSA 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.

MyProstateScore

The MyProstateScore (MPS) assay measures total serum PSA and post-DRE urine expression of *PCA3* and the *TMPRSS2::ERG* fusion gene.[309] Rearrangements of the *ERG* gene are found in approximately half of prostate cancers.[310] The *TMPRSS2::ERG* fusion specifically occurs at high frequency and appears to be an early event in prostate cancer development.[311] The role of *PCA3* in prostate cancer is discussed above. Early studies suggested that the combination of these two markers improved the prediction of prostate cancer on biopsy.[312]

An MPS validation study included 1244 individuals with planned biopsy (80% with no prior prostate biopsy) in a validation cohort.[309] The AUC for the prediction of any cancer was 0.751 for MPS, compared with 0.585 for PSA alone. For the prediction of Grade Group ≥2 cancer, the AUCs for MPS and PSA alone were 0.772 and 0.651, respectively.

Another validation cohort included 1525 patients from academic and community centers who were referred for initial biopsy.[313] MPS testing provided a sensitivity of 97% and an NPV of 98% for Grade Group ≥2 prostate cancer. The authors calculate that 33% of unnecessary biopsies could have been avoided by using the assay in biopsy decisions, while missing 3% of Grade Group ≥2 cancers.

The Panel believes that MPS 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.

MyProstateScore 2.0

In order to improve diagnostic accuracy for high-grade prostate cancer in individuals with elevated PSA levels, the MPS 2.0 assay was developed to measure 18 markers that are overexpressed in high-grade compared to low-grade prostate cancer.[314] Researchers analyzed post-DRE urine samples from 761 prebiopsy individuals with elevated PSA levels, and reported an AUC value for high-grade cancer of 0.81 (95% CI, 0.77–0.85) for MPS2, 0.82 (95% CI, 0.78–0.86) for MPS2+ (which accounts for prostate volume), and 0.74 (95% CI, 0.69–0.78) for MPS. External validation in 743 individuals revealed superior diagnostic accuracy for high-grade prostate cancers with MPS2 compared to the currently available options, which in practice would lead to a decrease in unwarranted biopsies and additional testing.

A validation study of MPS2 testing in urine specimens from individuals who did not undergo DRE concluded that MPS2 showed noteworthy value for detection of Grade Group ≥2 prostate cancer when measured against PSA-based tests.[315] MPS2 testing led to superior diagnostic accuracy with an AUC of 0.71 (95% CI, 0.65–0.77) compared to PSA alone, which had an AUC of 0.57 (95% CI, 0.50–0.64), and PCPT risk calculator with AUC of 0.62 (95% CI, 0.55–0.69). This relative improvement was further increased when incorporating biomarkers, clinical factors, and prostate volume model in MPS2 testing.

The Panel believes that MPS 2.0 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. This is a category 2B recommendation.

Stockholm3

Stockholm3 is a multivariate model that includes clinical variables (ie, age, first-degree family history of prostate cancer, previous biopsy), blood biomarkers (ie, PSA, fPSA, %fPSA, hK2, MIC1, MSMB), a genetic score based on 254 single-nucleotide polymorphisms (SNPs) and an explicit variable for the HOXB13 SNP, prostate volume, and DRE results.[316] When used in Swedish patients with PSA ≥3 ng/mL, the test reduced the number

of biopsies by 34% compared with PSA alone. Sensitivity was similar between the multivariate model and PSA alone.

In a prospective, population-based, randomized, open-label, noninferiority trial in Sweden (STHLM3-MRI), 2293 participants with either a PSA ≥3 ng/mL or a Stockholm3 score above the set threshold were randomly assigned 2:3 to either systematic prostate biopsies or to bpMRI followed by MRI-targeted and systematic biopsy in those with positive MRIs.[317] The AUC for the detection of Grade Group ≥2 prostate cancer was 0.76 (95% CI, 0.72–0.80) for Stockholm3 and 0.60 (95% CI, 0.54–0.65) for PSA. Screening with Stockholm3 and the MRI approach was associated with higher detection of Grade Group ≥2 prostate cancer, lower detection of low-grade cancers, and led to fewer biopsy procedures than screening using the PSA and systematic biopsy approach.

An extension of the Stockholm3 biomarker approach with systematic biopsies in those with a biomarker score ≥0.15 (biomarker group) and an approach using PSA followed by MRI in those with PSA ≥3 ng/mL studied the effect of utilizing both systematic and targeted biopsies (MRI-enhanced group).[318] Similarity in detection rates between these two methods would be advantageous for areas with limited MRI access. Of the 12,743 participants, 7609 were assigned to the MRI-enhanced group, and 5134 were assigned to the biomarker group. Both approaches had comparable detection rates for clinically significant prostate cancer, though a 1.9% increase in biopsies of indolent prostate cancers was observed in the biomarker group.

Similar conclusions were reached in a prospective, multicenter validation study involving 342 undiagnosed individuals scheduled for prostate biopsy. The report concluded that blood-based Stockholm3 testing demonstrated superior distinction (AUC, 0.77; 95% CI, 0.72–0.82) of clinically significant prostate cancer compared to PSA with an AUC of 0.66 (95% CI, 0.61–0.72).[319] Notably, the ≥0.11 cutoff score of Stockholm3

found 92% of clinically significant prostate cancers, 23% higher than the PSA ≥1.5 ng/mL cutoff (69%).

The Panel believes that Stockholm3 can be considered for patients prior to biopsy who are thought to be at higher risk for clinically significant prostate cancer.

Additional Biomarker Tests

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

MiR Sentinel Prostate Cancer Test

Wang and colleagues reported on the development and initial performance of a platform that interrogates small noncoding RNAs (sncRNAs) isolated from urinary exosomes.[320] The assay, MiR Sentinel Prostate Cancer Test, differentiates patients with prostate cancer from those with no evidence of prostate cancer. The test was developed on an

initial cohort of 235 participants and validated using a case-control sample of 1436 participants with a wide range of PSA values. Sensitivities and specificities for detection of high-grade cancer (Grade Group 2 or higher) were very high. This test awaits further validation, especially in the group of patients with negative DREs and PSAs in the range where most such tests are used (ie, 2.5–10.0 ng/mL).

Biopsy Technique

Initial Biopsy

Image-guided biopsy with targeting (preferred) or without targeting of lesions seen on pre-biopsy MRI is the recommended technique for prostate biopsy. When systematic biopsy is performed, the Panel recommends an extended-pattern, at least 12-core biopsy (sextant medial and lateral peripheral zone and lesion-directed). This extended-pattern scheme has been validated and results in enhanced cancer detection compared to sextant biopsy schemes.[321,322] 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.

Image-guided biopsy can be performed via a transrectal or a transperineal approach.[323-325] The PROMIS trial demonstrated improved detection of clinically significant cancer using transperineal template biopsy compared to transrectal biopsy.[215] Some data suggest that transperineal biopsy may be associated with a lower risk of sepsis and therefore a reduced need for antibiotics; however, data are conflicting (also see *Risks of Biopsy*, below).[326-328] However, extensive perineal template biopsies may lead to higher rates of other complications such as urinary retention. A definitive study comparing a more limited transperineal biopsy versus conventional transrectal biopsy has not been performed. The Panel views both approaches as reasonable options.

Targeted Biopsy Techniques

Interest in the use of novel imaging, particularly MRI, to guide needle placement during biopsy (see *Magnetic Resonance Imaging,* above) has been increasing over the last decade.

Targeted biopsy techniques include cognitive or visual targeting (guiding with ultrasound [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).[329-331] Data show that mpMRI followed by lesion targeting increases the detection of clinically significant, higher-risk (Grade Group ≥3) disease while lowering the detection of low-risk (Grade Group 1) disease. Data also suggest that different targeting techniques detect clinically significant prostate cancer at similar rates.[332]

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

Overall, the Panel believes that the data for the use of MRI and MRI-targeted biopsies in the initial biopsy setting are increasingly compelling. However, studies using both targeted and systematic sampling routinely demonstrate higher yield of clinically significant cancer with the combined approach and improved sensitivity.[229,333] Therefore, a combination of systematic and targeted procedures is preferred when MRI-targeting capabilities are available, at least at initial biopsy.

Repeat Biopsies

A negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. If clinical suspicion of cancer persists after a negative biopsy, consideration can be given to the use of mpMRI followed by an

appropriate targeted biopsy technique based on the results. In addition, biomarker testing can also be considered in these individuals to inform decisions regarding repeat biopsy (see *Biomarker Testing*, above).

Targeted Biopsy for Repeat Biopsy

After one or more negative image-guided biopsies, individuals who are considered at high risk (eg, those with persistently elevated or rising PSA) can be considered for MRI followed by targeted biopsy based on several studies showing improved detection of clinically significant prostate cancer in this setting.[207,334-340] Reported cancer detection rates by targeted fusion biopsies in individuals with previous negative biopsies range from 34% to 51%.[207,335-337] Studies that used direct MR guidance for targeted biopsies have reported similar cancer detection rates in those with previous negative biopsies: 41% to 56%.[338-340]

The targeted biopsy approach may lead to a higher rate of detection of clinically significant cancer in individuals with prior negative biopsy than repeat systematic biopsies, which lead to the identification of more low-risk tumors. For instance, in one retrospective cohort study, 105 participants with prior negative biopsies and elevated PSA underwent mpMRI followed by standard 12-core systematic biopsy and MR-US fusion-targeted biopsy regardless of MRI results.[336] Prostate cancer was found in 36 individuals (34%). In this study, 21 of 23 cancers (91%) identified by targeted biopsy were significant (Grade Group 2 or mean core length ≥4 mm), compared with 15 of 28 cancers (54%) identified by standard biopsy. Targeted biopsies missed clinically significant cancer in two patients compared with five missed clinically significant diagnoses by standard biopsies.

Another prospective study included 347 patients with findings suspicious for prostate cancer, many of whom had one or more previous negative biopsies.[207] All patients received an mpMRI, and those with abnormal findings proceeded to MRI-TRUS fusion-targeted biopsies. The outcome was defined as improved detection in targeted cores, with significantly more cancer detected in targeted cores than in systematic biopsies (30% vs. 8.2%). About 12% of those without MRI-suspicious lesions were diagnosed with intermediate-risk tumors. In this study, the cancer detection rate was 51% in individuals with previous negative biopsies.

In a prospective study, 583 patients (56% with prior negative biopsy) underwent mpMRI.[341] All participants received systematic 12-core biopsies, and those with lesions seen on MRI also received fusion-guided biopsies. Multivariate analysis revealed that a higher MRI suspicious score increased the likelihood of finding Grade Group ≥2 cancer by 3.3-fold (95% CI, 2.2–5.1; *P* < .0001).

A meta-analysis of 16 studies (1926 individuals) also showed that MRI-targeted biopsy improved detection of clinically significant prostate cancer in those with previous negative biopsies over standard TRUS biopsy.[342] In addition, the use of high-resolution micro-US has been compared to mpMRI and found to perform similarly for the detection of prostate cancer.[343]

Overall, the Panel believes that targeted biopsy techniques may help identify regions of cancer missed on prior biopsies and should be strongly considered in patients with a prior negative biopsy and persistent concern for cancer based on PSA levels and/or results of biomarker testing.[247]

Saturation Biopsy Techniques

In saturation biopsies, cores are collected systematically every few millimeters across the entire prostate to improve prostate cancer detection over that of a standard 12-core biopsy. In one study, transperineal prostate mapping biopsy was used to calculate biopsy density (the ratio of the total number of specimens retrieved to prostate volume) in 436 patients to determine the optimal sampling approach.[344] Results showed that biopsy density >1.5 was associated with a 1.5-fold higher rate of

prostate cancer diagnosis and a higher rate of detection of higher volume Grade Group 1 disease.

Saturation biopsies can be performed via transrectal or transperineal approaches, the latter of which is often image-guided (see *Targeted Biopsy for Repeat Biopsy*, above). The transrectal and transperineal saturation approaches seem to have similar rates of cancer detection.[345] 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* = .30).[346] 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.[347] In fact, studies reported zero or near-zero rates of sepsis in individuals biopsied with the transperineal approach.[348-350] Another possible benefit of the transperineal over the transrectal approach is more accurate risk assessment (cancer volume and grade).[351] However, the transperineal approach may be associated with a higher rate of urinary retention.[347] The transrectal approach can be performed routinely in the office whereas transperineal biopsy often requires more extensive local or systemic analgesia.

A study of transperineal template-guided mapping biopsy found detection rates of 55.5%, 41.7%, and 34.4% for those with 1, 2, and ≥3 previous negative biopsies, respectively.[352] Other groups have reported similar rates of detection using saturation biopsies in individuals with previous negative biopsies.[350,353,354]

Compared with an extended biopsy approach (12–14 cores), one prospective, non-randomized study found that transrectal saturation biopsy detected significantly more cancers in individuals with one previous negative biopsy (32.7% vs. 24.9%; *P* = .0075).[355] The detection of insignificant cancer did not differ significantly between the groups (40.1% vs. 32.6%; *P* = .20).

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

Risks of Biopsy

Biopsies are associated with the risk of complications, particularly antibiotic-resistant *Escherichia coli* infections.[356] The range of potential infectious complications includes urinary tract infection (UTI), epididymitis, orchitis, prostatitis, and sepsis. In fact, the 30-day risk of invasive *Escherichia coli* infections in U.S. hospitals from 2009 to 2016 was 5.0 per 1000 patients.[357]

Antimicrobial prophylaxis is therefore generally used with transrectal biopsies to prevent infections and reduce the need for antibiotics after the procedure, thus reducing the overuse of antibiotics.[358] Studies have reported that up to 78% of post-biopsy infections are resistant to fluoroquinolone, many of which are also resistant to other antibiotics.[357,359,360] In addition, the FDA labels for drugs in this class include additional warnings about disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system; risk of ruptures or tears in the aorta blood vessel; serious low blood sugar levels; and mental health side effects.[361] The American Urological Association (AUA) acknowledges that fluoroquinolone prophylaxis should be considered with transrectal biopsy in some centers and under some clinical conditions.[358] Other options recommended by the AUA include first- and second-generation cephalosporin with or without aminoglycoside; and third-generation cephalosporin.[358]

Although these fluoroquinolones-resistant infections will respond to cephalosporins, measures are needed to prevent additional resistant strains. One strategy is to utilize stringent criteria for biopsy as outlined in

these guidelines. Another approach is the use of transperineal prostate biopsies, which may be associated with a lower risk of sepsis and a reduced need for antibiotics compared to a transrectal approach; however, data are conflicted.[326,327] Results from the prospective, randomized ProBE-PC clinical trial showed no statistical difference in infectious and noninfectious outcomes in individuals who underwent transrectal (n = 351) prostate biopsy versus transperineal (n = 367) prostate biopsy, indicating both methods to be clinically reasonable approaches. [328] Other proposed strategies include selectively targeted antibiotic prophylaxis with pre-biopsy rectal culture and selectively augmented prophylaxis with two antibiotics in patients at elevated risk for infections.[356,362]

Other morbidities associated with prostate biopsies include rectal bleeding, hematuria, vasovagal episodes, fever, hematospermia, and dysuria.[363,364] Furthermore, up to 90% of individuals undergoing a prostate biopsy have reported some discomfort during the procedure.[365] Both topical lidocaine gel and an injectable nerve block have been shown to be safe and efficacious for reducing discomfort.[366,367] 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.[368] Another small trial found the combination of lidocaine with pelvic plexus block to be most effective at relieving pain associated with prostate biopsy.[369] More recently, a randomized trial compared peri-prostatic nerve block with subcutaneous perineal anesthesia and intrarectal lidocaine gel with total intravenous anesthesia in 216 patients receiving a TRUS-guided transperineal prostate biopsy.[370] The combination treatment resulted in less pain during the biopsy, shorter operation times ($P < .05$), more stable hemodynamics and respiratory status, and fewer surgical complications ($P < .05$).

These minor anesthetic techniques greatly enhance the acceptability of the procedure, particularly with extended templates and saturation techniques, and should be considered in all patients.[371] For situations such as individuals with anal strictures, those who do not readily tolerate biopsy under local anesthesia, or patients who have been inadequately blocked with a periprostatic injection, deep sedation or general anesthesia may be advantageous.

Summary of NCCN Recommendations for Early Detection

General Considerations

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

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

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

- Prostate cancer risk factors, such as family history, presence of inherited mutations, and African ancestry, should be considered before decisions are made concerning the initiation of an early

detection program (see *Screening in Populations With Elevated Risk*, above).

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

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

- A thorough discussion on the potential benefits and harms of testing must be carried out between the physician and the potential participant as outlined in the algorithm. Patients should be informed that the purpose of early detection is to find aggressive cancers, that early detection often detects low-risk cancers, and that such low-risk cancers may not need treatment but can be managed by active surveillance. Decision aids are available.[372-374]

- 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 individuals aged 45 to 75 years who are deemed to be at average risk based on the results of

RCTs. Baseline testing may be complemented by DRE. An elevated PSA should be confirmed by repeat testing.

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

- The Panel recommends a range of testing frequency between 1 and 4 years, depending on the age of the individual, the PSA levels, results of DRE (if done), and whether the patient is at elevated risk for prostate cancer.

- The Panel strongly recommends that mpMRI be performed before biopsy if available. Consideration may be given to various biomarker tests that improve biopsy specificity such as %fPSA, 4Kscore, SelectMDx, ExoDx Prostate, PHI, MPS, IsoPSA, MPS 2.0, and Stockholm3 before biopsy in those with serum PSA levels of >3 ng/mL who desire more specificity. PHI, %fPSA, 4Kscore, ConfirmMDx, PCA3, MPS, IsoPSA, and MPS 2.0 are also options in individuals thought to be higher risk despite a negative prostate biopsy.

- Panel members agree that a decision to perform a biopsy should not be based on a PSA cut point alone, but should incorporate other important clinical variables including age, family history, PSA kinetics, ancestry, health status, and patient preference, as well as results of mpMRI and/or biomarker tests.

- Patients with a high suspicion for clinically significant cancer should undergo image-guided biopsy via transrectal or transperineal approach. The Panel recommends that MRI targeting be used routinely in those centers with availability.

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

Management of Biopsy Results

Cancer

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

Intraductal Carcinoma Without Invasive Cancer

Intraductal carcinoma (IDC) represents an independent adverse pathologic factor in both radical prostatectomy and needle biopsy specimens that may influence disease response to current therapeutic regimens for advanced-stage prostate cancer. In radical prostatectomy, IDC correlates with other adverse pathologic features in the associated invasive prostate cancer, including higher Gleason score, larger tumor volume, and greater probability of extraprostatic extension, seminal vesicle invasion, and pelvic lymph node metastasis; it also independently predicts biochemical recurrence, progression-free survival, and cancer-specific mortality after radical prostatectomy.[375-383]

In biopsy specimens, IDC is typically seen with high-grade, high-volume prostate cancer and is associated with adverse findings in radical prostatectomy and poor outcomes. IDC diagnosed in prostate biopsies provided an independent prognostication of early biochemical recurrence, cancer-specific survival, survival in patients with distant metastasis at presentation, and the development of metastases after radiation therapy in intermediate- and high-risk prostate carcinoma.[384-386] IDC may be resistant to current therapeutic regimens for aggressive prostate cancer and may require a multimodal approach and novel therapy.[387]

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

Atypical Intraductal Proliferation Without Invasive Cancer

Intraductal proliferations may show a greater degree of architectural complexity and/or cytologic atypia than typical high-grade prostatic intraepithelial neoplasia (HGPIN; see below), yet they fall short of the strict diagnostic threshold for IDC. The preferred terminology for these lesions is "atypical intraductal proliferation (AIP)."[388-390] When diagnosed on needle biopsy, AIP is potentially considered a marker of unsampled cancer, and it is associated with a 50% increased risk of invasive carcinoma and/or IDC on repeat biopsy.[390,391] One study found that prostate cancer associated with AIP had worse pathologic features than prostate cancer associated with HGPIN.[380] Another study found that AIP-associated prostate carcinoma had similar clinicopathologic features to IDC-associated carcinoma.[389]

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

Other Notable Pathologic Features and Benign Results

Approximately 10% of patients undergoing biopsy will be found to have HGPIN.[392] 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.[393-395] Interestingly, the rates of cancer with repeat biopsy in patients with HGPIN 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.[396]

Atypia are characterized by glands that either architecturally or cytologically in some ways resemble prostatic adenocarcinoma, but lack full criteria for malignancy. They are distinct from HGPIN because they lack a basal cell layer. Atypia are either diagnosed with descriptive terminology or synonymously designated as atypical small acinar proliferation (ASAP).[397,398] Unlike HGPIN, ASAP is not a distinct pathologic diagnosis; rather it represents either benign mimickers of prostate cancer or cancer that lacks sufficient architectural or cytological atypia to warrant a definitive malignant diagnosis. Approximately 5% of patients receive a biopsy result of atypia. 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%, with the most likely area of cancer detection residing in the prostate area demonstrating atypia from the initial biopsy.[399,400]

Most prostate biopsy results are benign; however, a negative prostate biopsy does not preclude the presence of cancer. Thus, patients with benign results, as well as those with HGPIN or ASAP, may have prostate cancer and require follow-up. However, a balance is needed between maximizing the identification of clinically significant cancer and minimizing over-testing and overdiagnosis. Studies have shown that 4% to 9% of patients with ASAP, HGPIN, or benign biopsy results receive a diagnosis of Grade Group ≥2 prostate cancer on repeat biopsy, with no significant difference between these groups.[395,397,401-403] The rates of Grade Group 1 prostate cancer on repeat biopsy are 24% to 30%.[395,397,402,403] Furthermore, the prostate cancer-specific mortality rate in individuals with initially negative biopsy results is low. In a Danish study, the 15-year prostate cancer-specific mortality rate of patients with an initially negative biopsy was 1.3% for those with PSA <10 ng/mL and 4.6% for those with PSA >20 ng/mL.[404]

For patients with benign biopsy results, atypia suspicious for cancer, or HGPIN, recommendations depend on whether there was a prior high-quality mpMRI. For those with a prior high-quality mpMRI , PSA and DRE are recommended at 12- to 24-month intervals. Certain biomarker tests can also be considered (see *Biomarker Testing*, above). For those without prior high-quality mpMRI, biomarker testing and/or mpMRI should be considered. For atypia, repeated biopsy in 12 to 24 months with relative increased sampling of the atypical site should be considered. For all these patients, a repeat prostate biopsy with refined biopsy techniques is recommended if there is a high suspicion of cancer. Characteristics that increase the suspicion of cancer after a negative biopsy are a positive mpMRI, a persistently high PSA, a shorter PSA doubling time, a high PSA density, and/or an abnormal DRE.[405-407]

Summary

Since the early 1990s, many variants of the PSA assay have been introduced in attempts to increase the sensitivity of early detection programs or cancer detection while maintaining specificity (elimination of

unnecessary biopsies). These NCCN Guidelines recommend a method by which individuals and their physicians can use these techniques rationally for the early detection of prostate cancer. These guidelines are not designed to provide an argument for the use of population early detection programs for prostate cancer. Rather, they are meant to provide a vehicle by which early detection efforts can be practiced in an evidence-based, systematic fashion in patients who choose to participate in such programs. Whether to treat a patient upon diagnosis is beyond the scope of these guidelines (see the NCCN Guidelines for Prostate Cancer at www.NCCN.org).

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

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

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