National Comprehensive Cancer Network®

NCCN Harmonized Guidelines™ for Sub-Saharan Africa

Prostate Cancer Early Detection

Version 2.2024 — July 2, 2024

NCCN.org

Continue

***Kelvin A. Moses, MD, PhD / Chair** ω
Vanderbilt-Ingram Cancer Center

***Preston C. Sprenkle, MD / Vice Chair** ω
Yale Cancer Center/Smilow Cancer Hospital

Clinton Bahler, MD, MS ω
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Geoffrey Box, MD ω
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Sigrid V. Carlsson, MD, PhD, MPH &
Memorial Sloan Kettering Cancer Center

William J. Catalona, MD ω
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Douglas M. Dahl, MD ω
Mass General Cancer Center

Marc Dall'Era, MD ω
UC Davis Comprehensive Cancer Center

John W. Davis, MD ω
The University of Texas MD Anderson Cancer Center

Bettina F. Drake, PhD, MPH &
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Scott Eggener, MD ¶
The UChicago Medicine Comprehensive Cancer Center

Jonathan I. Epstein, MD ≠
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Ruth B. Etzioni, PhD &
Fred Hutchinson Cancer Center

Thomas A. Farrington, BSEE ¥
Prostate Health Education Network, Inc.

Isla P. Garraway, MD, PhD ω
UCLA Jonsson Comprehensive Cancer Center

David Jarrard, MD ω
University of Wisconsin Carbone Cancer Center

Eric Kauffman, MD ω
Roswell Park Comprehensive Cancer Center

Deborah Kaye, MD, MS ω
Duke Cancer Institute

Adam S. Kibel, MD ω
Dana-Farber/Brigham and Women's Cancer Center

Chad A. LaGrange, MD ¶ ω
Fred & Pamela Buffett Cancer Center

Paul Maroni, MD ω
University of Colorado Cancer Center

Lee Ponsky, MD ω
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Brian Reys, MS, CGC Δ
UT Southwestern Simmons Comprehensive Cancer Center

Simpa S. Salami, MD, MPH ω
University of Michigan Rogel Cancer Center

Alejandro Sanchez, MD ω
Huntsman Cancer Institute at the University of Utah

Tyler M. Seibert, MD, PhD §
UC San Diego Moores Cancer Center

Terrence M. Shaneyfelt, MD, MPH Þ
O'Neal Comprehensive Cancer Center at UAB

Marc C. Smaldone, MD, MSHP ω
Fox Chase Cancer Center

Geoffrey Sonn, MD ω
Stanford Cancer Institute

Mark D. Tyson II, MD, MPH ω
Mayo Clinic Comprehensive Cancer Center

Neha Vapiwala, MD §
Abramson Cancer Center at the University of Pennsylvania

Robert Wake, MD ω
St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

Samuel Washington III, MD, MAS ω
UCSF Helen Diller Family Comprehensive Cancer Center

Alice Yu, MD, MPH ω
Moffitt Cancer Center

Bertram Yuh, MD, MS ω
City of Hope National Medical Center

NCCN Guidelines Panel Disclosures

NCCN
Deborah Freedman-Cass, PhD
Megan Lyons, MS

Continue

& Epidemiology	§ Radiotherapy/Radiation oncology
Δ Genetic counseling	¶ Surgery/Surgical oncology
Þ Internal medicine	ω Urology
† Medical oncology	* Discussion Section Writing Committee
≠ Pathology	
¥ Patient advocacy	

AFRICAN CANCER COALITION REPRESENTATIVES

Abubakar Bello M, MD, FMCR, FICS/Chair † §
National Hospital Abuja, and
Federal University of Health Sciences, Azare
Nigeria

James Edward Mensah, MBChB, FWACS, FGCS/Vice Chair ω
Korle Bu Teaching Hospital
Ghana

Munir Aman, MD †
Addis Ababa University
Ethiopia

Chimwemwe M.K. Banda, MMed (Rad Onc), MBBS, MPH † §
Malawi National Cancer Centre - KCH
Malawi

Ahmed Rufai Isah, MBBS, FCNP (South Africa), MMED (Nuclear Medicine) φ
National Hospital Abuja
Nigeria

Sikudhani Muya, MD, FCROSA, Mmed (Rad Onc) §
Ocean Road Cancer Institute
Tanzania

Edouard Ngendahayo, MD, MMed ω
King Faisal Hospital
Rwanda

Nomsa Tsikai, MBChB, MMed (Rad Onc) † §
Harare Oncology Centre
Zimbabwe

NCCN
Crystal Denlinger, MD †

Kelvin A. Moses, MD, PhD/Chair ω
Vanderbilt-Ingram Cancer Center

The harmonization process is supported by a collaboration with the African Cancer Coalition and the American Cancer Society through the Allied Against Cancer alliance

AFRICAN CANCER COALITION
American Cancer Society®
ALLIED AGAINST CANCER®

Continue

Þ Internal medicine
† Medical oncology
φ Nuclear Medicine
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
ω Urology

Endorsements of the NCCN Harmonized Guidelines™ for Sub-Saharan Africa

Uganda Cancer Institute

Federal Ministry of Health, Ethiopia

Federal Ministry of Health, Nigeria

Mbeya Zonal Referral Hospital, Tanzania

Ocean Road Cancer Institute, Tanzania

Kilimanjaro Christian Medical Center, Tanzania

Government of Malawi

Ministry of Health, Liberia

Cancer Diseases Hospital, Ministry of Health, Zambia

Continue

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

See NCCN Harmonized Guidelines™ Table of Contents for other NCCN Harmonized Guidelines™ for Sub-Saharan Africa. The most recent version of the NCCN Guidelines is available at www.NCCN.org.

NCCN HARMONIZED GUIDELINES FOR SUB-SAHARAN AFRICA DEFINITIONS

THE NCCN HARMONIZED GUIDELINES™ FOR SUB-SAHARAN AFRICA ARE REPRESENTED AS FOLLOWS:
Black Text: Generally available standard of care
Gray Text: Highly advanced/optimal care that may be costly, technically challenging, and/or have a lesser impact on oncologic outcome
Italicized Blue Text: Regional options that may be considered when availability precludes general standard of care
Gray Text with ~~Strikethrough~~: Indicates care options that are not feasible or available in Sub-Saharan Africa at this time

Note: Drugs and biologics included in the NCCN Guidelines® are approved by the United States Food and Drug Administration (FDA). Alternate agents based on the local regulations and availability may be substituted provided evidence supports their efficacy and safety. Generic drugs should be used only when studies have proven bioequivalence and the drugs have met the same standards for identity, strength, purity, and quality as the innovator drugs. The WHO Model Lists of Essential Medicines can be found here: http://www.who.int/medicines/publications/essentialmedicines/en/.

PRINCIPLES OF CANCER CARE

- *Patients should be referred to centers that provide the highest level of care for a given clinical presentation.*

- *Added lower level care options should be considered only when referral or access to higher levels is not possible*
  - *Standards of care are based on best reported achievable outcomes. Issues of cost, regulatory environment, and medical education and training are considerations that may affect treatment selection.*
  - *Multidisciplinary care is always recommended.*

- *Delays in treatment reduce the effectiveness of treatment, so efforts should be made to expedite investigations and referrals to reduce waiting time before treatment initiation.*

- *Universal health coverage should cover the full continuum of care, from diagnosis through end-of-life care or survivorship.*

Note: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUMMARY OF UPDATES TO THE HARMONIZED GUIDELINES

NCCN Harmonized Guidelines™ for Sub-Saharan Africa: Prostate Cancer Early Detection have been updated to Version 2.2024 from Version 2.2021.
The changes are based on the updates to the NCCN Guidelines for Prostate Cancer Early Detection, Version 2.2024.

Note: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

INTRODUCTION

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

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

**See NCCN Harmonized Guidelines™ for Sub-Saharan Africa: Prostate Cancer.*

Baseline Evaluation (PROSD-2)

Note: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BASELINE 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]

→

RISK ASSESSMENT

Start risk and benefit discussion about offering prostate cancer early detection:
- Baseline PSA[g]
- Consider baseline digital rectal examination (DRE)[g]

→ 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]
- Those with concerning family or personal history[a,c]

or

Age 45–75 y for patients with average risk

EARLY DETECTION EVALUATION

- Patients with average risk and PSA <1 ng/mL,[e] DRE normal (if done) → Repeat testing at 2- to 4-year intervals[j]
- Patients with high risk and PSA ≤3 ng/mL,[e] DRE normal (if done) and Patients with average risk and PSA 1–3 ng/mL,[i] 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] and/or very suspicious DRE → Further Evaluation and Indications for Biopsy (PROSD-3)

→ Age >75 y, in select patients (category 2B)[h]
- PSA <4 ng/mL,[e] DRE normal (if done), and no other indications for biopsy → Repeat testing at 1 to 3-year intervals or Consider discontinuing screening if clinically appropriate[j]
- PSA ≥4 ng/mL[e] or very suspicious DRE → Further Evaluation and Indications for Biopsy (PROSD-3)
- Not screened[h]

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

Note: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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. 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. Patients with a suspicious family history should undergo genetic testing. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (CRIT-1) and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (LS-1). Page EC, Eur Urol 2019;76:831-842; Giri VN, et al. J Clin Oncol 2020;38:2798-2811.

[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*). Such risk genes include, but are not limited to, *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, and *TP53*. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. 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.

[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, increased prostate cancer mortality, and earlier age of diagnosis compared to white individuals. This is attributable to a greater 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 social determinants of health and lack of access to care, 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). 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.

Footnotes continued on PROSD-2B

Note: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES

[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.

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

FURTHER EVALUATION AND INDICATIONS FOR BIOPSY[k]

MANAGEMENT

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

→

- **Multiparametric MRI (mpMRI) (category 1) if available[l]**
- Consider biomarkers that improve the specificity of screening[m]

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

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

** Information from mpMRI should be used to inform regions from which to take extra samples during biopsy (cognitive targeting).*

[k] 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.

[l] A negative MRI does not exclude the possibility of cancer. Consider biomarkers and/or PSA density when deciding whether to avoid a biopsy in an individual with a negative mpMRI result.

[m] 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.

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

[o] 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.

[p] 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: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF BIOPSY RESULTS

Cancer → **NCCN Guidelines for Prostate Cancer***

Intraductal carcinoma (IDC) without invasive carcinoma[q] → **NCCN Guidelines for Prostate Cancer***

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

Atypia, suspicious for cancer / **High-grade prostatic intraepithelial neoplasia (PIN)[s,t]** / **Benign[s,t,u,v]** →

- **If no prior high-quality mpMRI:**
  - **Consider** biomarkers that improve the specificity of screening[u] and/or **mpMRI[s]**
  - **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- *6 to 12* **month intervals**
    and
  - Consider biomarkers that improve the specificity of screening[u]
- **Repeat prostate biopsy in 6–12 months** with refined biopsy techniques,** **if high suspicion of cancer[v]**

** See NCCN Harmonized Guidelines™ for Sub-Saharan Africa: Prostate Cancer.*
*** Information from mpMRI should be used to inform regions from which to take extra samples during biopsy (cognitive targeting).*

[q] 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.

[r] 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.

[s] 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.

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

[u] 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).

[v] 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: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ABBREVIATIONS

AIP	**atypical intraductal proliferation**
DRE	**digital rectal exam**
H&P	**history and physical**
IDC	**intraductal carcinoma**
mpMRI	**multiparametric MRI**
MPS	**MyProstateScore**
PCPT	**Prostate Cancer Prevention Trial**
PHI	**Prostate Health Index**
PIN	**prostatic intraepithelial neoplasia**
PSA	**prostate-specific antigen**
TRUS	**transrectal ultrasound**

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Note: This is the NCCN Harmonized Guidelines™ for Sub-Saharan Africa. For definitions, see page DEF-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Prostate Cancer Early Detection

Discussion

This discussion corresponds to the NCCN Guidelines for Prostate Cancer Early Detection. Last updated: March 06, 2024

Table of Contents

NCCN Guidelines Version 2.2024
Prostate Cancer Early Detection

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 29% of all new diagnoses in males, and is the second leading cause of cancer deaths in American men.[1] In 2024, it is estimated that 299,010 Americans will be diagnosed with prostate cancer and 35,250 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 greater than 10 ng/mL confer a greater than 67% likelihood of biopsy-detectable prostate cancer, and only about 18% of patients with PSA in the 4 to 10 ng/mL range have a subsequent positive biopsy.[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 or less 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 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 greater than 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 control.[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 more than 80,000 records of patients with prostate cancer and found that use of 5-ARI before diagnosis was associated with delayed diagnosis, higher stage at diagnosis, higher prostate cancer–specific mortality, and higher all-cause mortality.[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 history.

A health survey on 12,457 people visiting a prostate cancer screening clinic showed that greater than 20% took herbal supplements, while only 10% took a prescription medication (such as finasteride) to help treat lower urinary tract symptoms.[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]

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.[71,72] 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[73] 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.[74] 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).[75] 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.[76]

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%.[77] 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%.[78]

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.[79]

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.[80] 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.[81] 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.[82]

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.[83] 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.[84]

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.[85,86] 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.[87]

An analysis, which endeavored to account for the increased screening and diagnostic workup in the control arms of the PLCO and ERSPC, found that PSA screening lowered the risk for prostate cancer death in both trials by similar amounts (by an estimated 25% to 31% in PLCO and by an estimated 27% to 32% in ERSPC).[88]

In a subset analysis of PLCO reported by Crawford and colleagues,[89] 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.[90]

CAP Trial

The results of the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) were reported in 2018.[91] 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. Although this trial had several very important strengths, it had limitations as well. Only a single PSA test was used, a standard 10-core biopsy was undertaken, the median follow-up was 10 years, and 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.

Trial Limitations

In addition to the limitations of the PLCO trial noted previously, these randomized controlled trials (RCTs) also share at least three additional limitations. First, they did not address the potential benefit of screening in those with high-risk factors. For instance, less than 5% of PLCO participants were of African descent and only 7% reported a family history of prostate cancer.[92] 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.[73]

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.[93]

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.[94] A study by Lilja and colleagues[95] 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.[96]

Another report clarified associations of age with the long-term risks of metastases.[97] 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.[98] 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.[99] 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 $P \leq .004$).

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.[100] 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 less than 1 ng/mL had a very low risk for cancer at 4 and 8 years (0.23% and 0.49%).[101] Other studies have shown that PSA values at younger ages strongly predict the development of or death from prostate cancer.[102,103] 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.[103] 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.[97-99,102,104,105] 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.[106] 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.[107] 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.[108] 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.[109] 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 less than 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 up to 70 years, several panelists favored stopping testing at age 70 years.

However, other data would suggest a benefit to screening beyond 70 years. A study of 4561 patients who underwent radical prostatectomy found that those >70 years were more likely to have higher grade and stage of disease and worse survival compared to those ≤70 years.[110] Others have published similar findings.[111] 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%).[112] 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 before age 75 years.[113] 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.[114] 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[108] 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[103] examined the relationship between baseline PSA at age 60 years and the future risk of prostate cancer death or metastases and found that those with a PSA level below the median (<1 ng/mL) were unlikely to develop clinically significant prostate cancer (0.5% risk of metastases and 0.2% risk of prostate cancer death). Similarly, in a study of 849 individuals in the Baltimore Longitudinal Study of Aging (BLSA), no individuals aged 75 to 80 years with a PSA less than 3.0 ng/mL died of prostate cancer.[115] 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.

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.[116-122] 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.[123,124] 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.[118,119] 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).[125] A population-based study in Sweden found that

the risk for the development of prostate cancer increased with the number of affected relatives.[126] 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.[121,127,128]

Prostate cancer risk is also elevated in patients with a family history of breast cancer.[129,130] 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.[131] Welch and Brawley refer to this phenomenon as “self-fulfilling risk factors” in cancers that are “scrutiny-dependent.”[132]

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*.[133] 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.[134-136] *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.[137]

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

In addition, patients who meet hereditary risk assessment criteria established in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org) should be referred for genetic counseling/testing as appropriate.[138] Commercial panels are now available to assess most of the main high-penetrance prostate cancer risk genes (*BRCA1, BRCA2, ATM, MLH1, MSH2, MSH6, HOXB13, CHEK2, NBN, PALB2, RAD51D,* and *TP53*).

Information regarding the status of high-risk germline mutations should be used as part of the discussion about prostate cancer early 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*.[139] 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.[140-145] Age of onset and aggressiveness of prostate cancer in these individuals do not generally appear to be different than in sporadic cases.[141,144] Interestingly, a study of 524 families with pathogenic germline

PALB2 alterations found no evidence for an increased risk of prostate cancer.[146]

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).[139] 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.[147] It is also associated with an approximately 9-fold increased risk of prostate cancer.[148] Data also suggest that individuals with germline *TP53* mutations are more likely to develop aggressive prostate cancer.[148]

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.[149,150] These mutations have been associated with an increased risk for prostate cancer in numerous reports.[151-160] 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.[152,154,155,160-163] 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.[164-169]

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.[170] 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 and a 36% to 39% increase in prostate cancer mortality compared with white individuals.[120,171,172] Data also show that Black individuals are more likely to have aggressive prostate cancer and to be diagnosed with more advanced disease.[173-176] Modeling studies indicate that Black individuals likely have a higher incidence of preclinical disease and an increased risk of metastatic progression than white individuals.[177] 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. [178] 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.[179] 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,[180] whereas an older SEER analysis found that African American individuals were diagnosed at an average of 3 years younger than white American individuals.[181] 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.[182] 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.[181]

The main drivers for these racial inequities are likely lower rates of prostate cancer screening, diagnostic procedures, and overall access to health care; inadequate health insurance coverage; and other factors related to social determinants of health (eg, environmental exposures; patient and physician behaviors; delays in diagnosis; suboptimal treatment).[176,183-188] Further evidence supports the likelihood that such inequities are not related to race itself or differences in the frequency of tumor-acquired genomic variants.[189] In fact, data show that Black patients who receive equitable prostate cancer treatment have similar outcomes to white patients.[190]

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.[92] In the ERSPC trial, no information on ancestry or family history was reported.[71]

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).[191] 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.[105] 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.[192] 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.[109]

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:

- Prostate cancer early detection is recommended at age 40 for *BRCA2* carriers.
- It is reasonable for individuals with other germline mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year.
- Individuals with a suspicious family cancer history (as defined in the Guidelines, above) should 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).[63,193] 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. The panel strongly recommends that multiparametric MRI (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 multiparametric MRI. Therefore, it is not known with certainty how such tests could be applied in optimal combination.

An abnormal DRE in this setting of elevated PSA has a high predictive value,[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.[68,194-200] 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.[201] However, such calculators have not been assessed in RCTs, and cut-points of risk associated with reductions in prostate cancer mortality remain unknown. Such calculators have as much value in determining who might not need biopsy as in identifying those at higher risk. At this time, the panel does not recommend the use of risk calculators *alone* to determine whether biopsy is indicated. Clinical judgment and patient preferences need to be taken into consideration.

Magnetic Resonance Imaging

Considerable interest exists in using multiparametric MRI both pre-biopsy to select patients for biopsy and during biopsy to guide needle placement.[202-209] The goals of using multiparametric MRI in these settings include reducing the number of individuals undergoing biopsy, reducing the detection of indolent disease (and thus the risks of 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 multiparametric MRI followed by TRUS biopsy and perineal template mapping biopsy.[210] 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.[211] 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.[212-216]

MRI-FIRST was a prospective, multicenter, paired diagnostic study conducted at 16 centers in France.[217] 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 included 626 patients who were biopsy-naïve at four centers in the Netherlands: the 4M study.[218] 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.[219] 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.[220] 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.[221] Participants were randomized to undergo MRI followed by targeted biopsy only if PI-RADS score was 3 or higher (MRI-TB) or systematic TRUS biopsy. The primary outcome measure, the proportion of 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.[222] 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; relative risk, 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%; relative risk, 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%). Data from this study thus show an approximately 50% decreased risk of detecting clinically insignificant prostate cancers when systematic biopsies are omitted with intermediate-risk cancers missed in approximately 0.2% of individuals. 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.[204,223-227] 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.[206,217,228] 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 multiparametric MRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion-targeted biopsy.[206] 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 multiparametric MRI group or a standard biopsy group.[228] Participants in the multiparametric MRI group had targeted fusion biopsies if suspicious lesions were seen. Otherwise, they received standard biopsies. More clinically significant prostate cancers were detected in the multiparametric MRI arm (43.9% vs. 18.1%; $P < .001$).

Similar to the studies above, multiple retrospective studies have shown that adding MRI-targeted biopsy to systematic biopsy increases the yield of clinically significant prostate cancer over systematic biopsy alone. A 2019 Cochrane systematic review identified 18 cross-sectional studies that compared template-guided biopsy with MRI only, MRI-targeted biopsy, MRI with or without MRI-targeted biopsy, and/or systematic biopsy for the detection of Grade Group ≥2 prostate cancer.[229] 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.[230]

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% to 49%), but some of these people have clinically significant disease that would be missed (2% to 14% of the study populations).[211,217,218,221,231,232] 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.[217,233]

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.[234-236] 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/Reporting-and-Data-Systems/PI-RADS).

At this time, the panel strongly recommends that a multiparametric MRI (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% to 98%).[211,217,218,221,231,232] 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.[213,237,238]

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 multiparametric MRI 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 multiparametric MRI 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).[239]

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 further define 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 have been validated in peer-reviewed, multi-site studies using an independent cohort of patients, as outlined in the Guidelines above and discussed in detail below. The extent of validation of these tests across diverse populations varies (see below). Results of biomarker assays can be complex and should be interpreted with caution. Referral to a specialist should be considered, and multiparametric MRI is also a consideration in these same patients. It is not yet known, with certainty, how biomarker tests can be applied in optimal combination with MRI.

Head-to-head comparisons have been performed for some of these tests, used independently or in combinations in the initial or repeat biopsy settings, but sample sizes were often small and results varied.[240-252] Therefore, the panel believes that no biomarker test can be recommended over any other at this time. Furthermore, a biomarker assay can be done alone or in addition to multiparametric MRI/refined biopsy techniques.[253,254] The optimal order of biomarker tests and imaging is unknown, and it remains unclear how to interpret results of multiple tests in individual patients—especially when results are contradictory. However, several more recent studies suggest that upfront biomarker testing with conditional MRI may be an efficient and effective way to assess those with a persistently elevated PSA.[254-256]

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.[257]

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.[258,259] 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.[260]

PSA density has also been shown to correlate with prostate cancer presence and aggressiveness, and may predict adverse pathology and biochemical progression after treatment.[261,262] 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.[263-266] 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%.[263] Participants with a score of ≥25 were 4.6 times more likely to have a positive repeat biopsy than those with a score <25.

Results were reported from an NCI Early Detection Research Network (EDRN) validation study of the PCA3 urinary assay in 859 individuals scheduled for a diagnostic prostate biopsy in 11 centers.[267] 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 CMS (Centers for Medicare & Medicaid Services) 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.[268-270] 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.[271] 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.[272] 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.[253,273-275]

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%; $P < .0001$).[276] 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%.[277]

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.[278,279] 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).[280] 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).[281] 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.[282] In addition, a correlation between 4Kscore risk category and Gleason score was seen ($P < .01$). A meta-analysis that included 12 clinical validation studies (11,134 patients) led to a calculated pooled AUC for discrimination of Grade Group ≥2 prostate cancer of 0.81 (fixed effects 95% CI, 0.80–0.83).

The panel consensus is that the test can be considered for patients prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk for clinically significant prostate cancer. It is important for patients and their urologists to understand, however, that no optimal 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 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.[283] The NPV was 90% (95% CI, 87%–93%). In a multivariate analysis, ConfirmMDx was predictive of patient outcome (OR, 3.17; 95% CI, 1.81–5.53). A similar validation study was performed in the United States using archived tissue from 350 patients with negative biopsies who had repeat biopsies within 24 months.[284] The NPV was 88% (95% CI, 85%–91%), and the test was again found to be predictive of outcomes on multivariate analysis (OR, 2.69; 95% CI, 1.60–4.51).

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

ExoDx Prostate (IntelliScore)

ExoDx Prostate (IntelliScore), also called EPI, evaluates a urine-based 3-gene exosome expression assay utilizing *PCA3* and *ERG* (V-ets erythroblastosis virus E26 oncogene homologs) RNA from urine, normalized to *SPDEF* (SAM pointed domain-containing ETS transcription factor). The background for these markers is supported by a number of studies, but the application to exosome detection is unique.[285] 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.[286] 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.[287] In the first phase of this study, the AUC was 0.70 for predicting Grade Group ≥2 cancer by EPI. Using the validated cut-point 15.6, the test has an NPV of 89%, reducing total biopsies by 20% and missing 7% of Grade Group ≥2 cancer. The second phase of this trial will be reported in the future.

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.[288] 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.[289,290] 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.[291] 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 multiparametric MRI results in 172 patients who had multiparametric MRI because of persistent clinical suspicion of prostate cancer or for local staging after positive biopsy.[292] The AUC of SelectMDx for the prediction of multiparametric MRI outcome was 0.83, whereas the AUC for PSA and PCA2 were 0.66 and 0.65, respectively.

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

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

IsoPSA

IsoPSA is a blood-based assay that uses an aqueous 2-phase system to partition and detect PSA isoforms in blood.[294] In a prospective, multicenter validation study, IsoPSA was assessed as a diagnostic biomarker test in 888 patients scheduled for prostate biopsy.[295] 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%.[296]

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.[297] Rearrangements of the *ERG* gene are found in approximately half of prostate cancers.[298] The *TMPRSS2:ERG* fusion specifically occurs at high frequency and appears to be an early event in prostate cancer development.[299] 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.[300]

An MPS validation study included 1244 individuals with planned biopsy (80% with no prior prostate biopsy) in a validation cohort.[297] 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.[301] 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.

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 (sncRNA) isolated from urinary exosomes.[302] 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).

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.[303] 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 biparametric MRI

followed by MRI-targeted and systematic biopsy in those with positive MRIs.[304] 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.

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.[305,306] 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.[307-309] The PROMIS trial demonstrated improved detection of clinically significant cancer using transperineal template biopsy compared to transrectal biopsy.[210] 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).[310-312] 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).[313-315] Data show that multiparametric MRI followed by lesion targeting increases the detection of clinically significant, higher-risk (Grade Group ≥3) disease while lowering the detection of low-risk (Grade Group 1) disease. Data also suggest that different targeting techniques detect clinically significant prostate cancer at similar rates.[316]

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.[223,317] Therefore, a combination of systematic and targeted procedures is preferred when MRI-targeting capabilities are available, at least at initial biopsy.

Repeat Biopsies

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

followed by an appropriate targeted biopsy technique based on the results. In addition, biomarker testing can also be considered in these individuals to inform decisions regarding repeat biopsy (see *Biomarker Testing*, 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.[202,318-324] Reported cancer detection rates by targeted fusion biopsies in individuals with previous negative biopsies range from 34% to 51%.[202,319-321] Studies that used direct MR guidance for targeted biopsies have reported similar cancer detection rates in those with previous negative biopsies: 41% to 56%.[322-324]

The targeted biopsy approach may lead to a higher rate of detection of clinically significant cancer in individuals with prior negative biopsy than repeat systematic biopsies, which lead to the identification of more low-risk tumors. For instance, in one retrospective cohort study, 105 participants with prior negative biopsies and elevated PSA underwent multiparametric MRI followed by standard 12-core systematic biopsy and MR-US fusion-targeted biopsy regardless of MRI results.[320] 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.[202] All patients received a multiparametric MRI, and those with abnormal findings proceeded to MRI-TRUS fusion-targeted biopsies. The outcome was defined as improved detection in targeted cores, with significantly more cancer detected in targeted cores than in systematic biopsies (30% vs. 8.2%). About 12% of those without MRI-suspicious lesions were diagnosed with intermediate-risk tumors. In this study, the cancer detection rate was 51% in individuals with previous negative biopsies.

In a prospective study, 583 patients (56% with prior negative biopsy) underwent multiparametric MRI.[325] 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.[326] 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.[327]

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.[239]

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.[328] Results showed that biopsy density greater than 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.[329] In fact, one study compared the approaches head-to-head and found similar cancer detection rates in the repeat biopsy setting (31.4% for transrectal vs. 25.7% for transperineal; $P = .3$).[330] 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.[331] In fact, studies reported zero or near-zero rates of sepsis in individuals biopsied with the transperineal approach.[332-334] Another possible benefit of the transperineal over the transrectal approach is more accurate risk assessment (cancer volume and grade).[335] However, the transperineal approach may be associated with a higher rate of urinary retention.[331] 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.[336] Other groups have reported similar rates of detection using saturation biopsies in individuals with previous negative biopsies.[334,337,338]

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%; $P = .0075$).[339] The detection of insignificant cancer did not differ significantly between the groups (40.1% vs. 32.6%; $P = .2$).

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

Risks of Biopsy

Biopsies are associated with the risk of complications, particularly antibiotic-resistant *Escherichia coli* infections.[340] 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.[341]

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.[342] Studies have reported that up to 78% of post-biopsy infections are resistant to fluoroquinolone, many of which are also resistant to other antibiotics.[341,343,344] 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.[345] The American Urological Association (AUA) acknowledges that fluoroquinolone prophylaxis should be considered with transrectal biopsy in some centers and under some clinical conditions.[342] Other options recommended by the AUA include 1st/2nd generation cephalosporin with or without aminoglycoside; and 3rd generation cephalosporin.[342]

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.[310,311] 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. [312] 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.[340,346]

Other morbidities associated with prostate biopsies include rectal bleeding, hematuria, vasovagal episodes, fever, hematospermia, and dysuria.[347,348] Furthermore, up to 90% of individuals undergoing a prostate biopsy have reported some discomfort during the procedure.[349] Both topical lidocaine gel and an injectable nerve block have been shown to be safe and efficacious for reducing discomfort.[350,351] 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.[352] Another small trial found the combination of lidocaine with pelvic plexus block to be most effective at relieving pain associated with prostate biopsy.[353] 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.[354] 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.[355] 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 pros and cons of testing must be carried out between the physician and the potential participant as outlined in the algorithm. Patients should be informed that the purpose of early detection is to find aggressive cancers, that early detection often detects low-risk cancers, and that such low-risk cancers may not need treatment but can be managed by active surveillance. Decision aids are available.[356-358]

- 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 deemed to be at average risk aged 45 to 75 years based on the results of RCTs. Baseline testing may be complemented by DRE. An elevated PSA should be confirmed by repeat testing.

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

- The panel recommends that frequency of testing be 2 to 4 years for those <75 years with serum PSA values below 1 ng/mL considered to be at average risk for prostate cancer. For those with PSA of 1 to 3 ng/mL at average risk, testing should occur at 1- to 2-year intervals. For those with elevated prostate cancer risk, the recommended testing interval for those with PSA ≤3 ng/mL is 1 to 2 years.

- The panel strongly recommends that multiparametric MRI 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, and IsoPSA before biopsy in those with serum PSA levels of >3 ng/mL who desire more specificity. PHI, %fPSA, 4Kscore, ConfirmMDx, PCA3, MPS, and IsoPSA 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 multiparametric MRI 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.[359-367]

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.[368-370] IDC may be resistant to current therapeutic regimens for aggressive prostate cancer and may require a multimodal approach and novel therapy.[371]

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 fall short of the strict diagnostic threshold for IDC. The preferred terminology for these lesions is "atypical intraductal proliferation (AIP)."[372-374] 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.[374,375] One study found that prostate cancer associated with AIP had worse pathologic features than prostate cancer associated with HGPIN.[364] Another study found that AIP-associated prostate

carcinoma had similar clinicopathologic features to IDC-associated carcinoma.[373]

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.[376] 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.[377-379] 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.[380]

Distinct from HGPIN in which a basal cell layer is present, atypia is characterized by glands that either architecturally or cytologically in some ways resemble prostatic adenocarcinoma, but lack full criteria for malignancy. These prostate cancer are either diagnosed with descriptive terminology or synonymously designated as atypical small acinar proliferation (ASAP).[381,382] 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% or more, with the most likely area of cancer detection residing in the prostate area demonstrating atypia from the initial biopsy.[383,384]

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.[379,381,385-387] The rates of Grade Group 1 prostate cancer on repeat biopsy are 24% to 30%.[379,381,386,387] 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 PSA >20 ng/mL.[388]

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 one, 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 12–24 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.[389-391]

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.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38230766.

2. Lifetime Risk of Developing or Dying From Cancer. American Cancer Society; Available at: https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html. Accessed January 18, 2024.

3. Negoita S, Feuer EJ, Mariotto A, et al. Annual report to the nation on the status of cancer, part II: Recent changes in prostate cancer trends and disease characteristics. Cancer 2018;124:2801-2814. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29786851.

4. PubMed Overview. National Library of Medicine; 2023. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed August 18, 2023.

5. Freedman-Cass DA, Fischer T, Alpert AB, et al. The value and process of inclusion: Using sensitive, respectful, and inclusive language and images in NCCN content. J Natl Compr Canc Netw 2023;21:434-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37156485.

6. Lavallee LT, Binette A, Witiuk K, et al. Reducing the harm of prostate cancer screening: repeated prostate-specific antigen testing. Mayo Clin Proc 2016;91:17-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26688045.

7. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998;279:1542-1547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9605898.

8. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156-1161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1707140.

9. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004;350:2239-2246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15163773.

10. Thompson IM, Ankerst DP, Chi C, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. JAMA 2005;294:66-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15998892.

11. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009;101:374-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19276453.

12. Aus G, Bergdahl S, Lodding P, et al. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007;51:659-664. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16934392.

13. Eggener SE, Large MC, Gerber GS, et al. Empiric antibiotics for an elevated prostate-specific antigen (PSA) level: a randomised, prospective, controlled multi-institutional trial. BJU international 2013;112:925-929. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23890317.

14. D'Amico AV, Roehrborn CG. Effect of 1 mg/day finasteride on concentrations of serum prostate-specific antigen in men with androgenic alopecia: a randomised controlled trial. Lancet Oncol 2007;8:21-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17196507.

15. Brawer MK, Lin DW, Williford WO, et al. Effect of finasteride and/or terazosin on serum PSA: results of VA Cooperative Study #359. Prostate 1999;39:234-239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10344212.

16. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192-1202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20357281.

17. Marberger M, Freedland SJ, Andriole GL, et al. Usefulness of prostate-specific antigen (PSA) rise as a marker of prostate cancer in men treated with dutasteride: lessons from the REDUCE study. BJU Int 2012;109:1162-1169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21699645.

18. Roehrborn CG, Andriole GL, Wilson TH, et al. Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostates in the Combination of Avodart and Tamsulosin trial. Eur Urol 2011;59:244-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21093145.

19. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12824459.

20. Unger JM, Hershman DL, Till C, et al. Using medicare claims to examine long-term prostate cancer risk of finasteride in the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2018;110:1208-1215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29534197.

21. Thompson IM, Jr., Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. N Engl J Med 2013;369:603-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23944298.

22. Goodman PJ, Tangen CM, Darke AK, et al. Long-term effects of finasteride on prostate cancer mortality. N Engl J Med 2019;380:393-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30673548.

23. Pinsky PF, Black A, Grubb R, et al. Projecting prostate cancer mortality in the PCPT and REDUCE chemoprevention trials. Cancer 2013;119:593-601. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22893105.

24. Wallerstedt A, Strom P, Gronberg H, et al. Risk of prostate cancer in men treated with 5alpha-reductase inhibitors-A large population-based prospective study. J Natl Cancer Inst 2018;110:1216-1221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29548030.

25. Sarkar RR, Parsons JK, Bryant AK, et al. Association of treatment with 5alpha-reductase inhibitors with time to diagnosis and mortality in prostate cancer. JAMA Intern Med 2019;179:812-819. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31058923.

26. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). J Clin Oncol 2004;22:1025-1033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15020604.

27. Barqawi A, Gamito E, O'Donnell C, Crawford ED. Herbal and vitamin supplement use in a prostate cancer screening population. Urology 2004;63:288-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14972473.

28. Carlsson S, Leapman M, Carroll P, et al. Who and when should we screen for prostate cancer? Interviews with key opinion leaders. BMC Med 2015;13:288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26612204.

29. McDonald ML, Parsons JK. The case for tailored prostate cancer screening: an NCCN perspective. J Natl Compr Canc Netw 2015;13:1576-1583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26656524.

30. Wilt TJ, Dahm P. PSA screening for prostate cancer: why saying no is a high-value health care choice. J Natl Compr Canc Netw 2015;13:1566-1574. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26656523.

31. Penson DF, Resnick MJ. Let's not throw the baby out with the bathwater in prostate cancer screening. J Clin Oncol 2016;34:3489-3491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27432920.

32. Pinsky PF, Prorok PC, Kramer BS. Prostate cancer screening - a perspective on the current state of the evidence. N Engl J Med 2017;376:1285-1289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28355509.

33. Shoag JE, Schlegel PN, Hu JC. Prostate-specific antigen screening: time to change the dominant forces on the pendulum. J Clin Oncol 2016;34:3499-3501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27432925.

34. Clegg LX, Li FP, Hankey BF, et al. Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology, and End Results) Program population-based study. Arch Intern Med 2002;162:1985-1993. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12230422.

35. Paquette EL, Sun L, Paquette LR, et al. Improved prostate cancer-specific survival and other disease parameters: impact of prostate-specific antigen testing. Urology 2002;60:756-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12429290.

36. Etzioni R, Gulati R, Tsodikov A, et al. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. Cancer 2012;118:5955-5963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22605665.

37. Chou R, LeFevre ML. Prostate cancer screening--the evidence, the recommendations, and the clinical implications. JAMA 2011;306:2721-2722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22203543.

38. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. JAMA 2015;314:80-82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26151271.

39. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;157:120-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22801674.

40. Barocas DA, Mallin K, Graves AJ, et al. Effect of the USPSTF grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. J Urol 2015;194:1587-1593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26087383.

41. Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US Preventive Services Task Force recommendation discouraging prostate-specific antigen-based screening. J Clin Oncol 2015;33:2416-2423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26056181.

42. Etzioni R, Gulati R. Recent trends in PSA testing and prostate cancer incidence: A look at context. JAMA Oncol 2016;2:955-956. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27010657.

43. Fedewa SA, Ward EM, Brawley O, Jemal A. Recent patterns of prostate-specific antigen testing for prostate cancer screening in the United States. JAMA Intern Med 2017;177:1040-1042. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28437537.

44. Halpern JA, Shoag JE, Artis AS, et al. National trends in prostate biopsy and radical prostatectomy volumes following the US Preventive Services Task Force guidelines against prostate-specific antigen screening. JAMA Surg 2017;152:192-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27806151.

45. Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. JAMA 2015;314:2054-2061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26575061.

46. Houston KA, King J, Li J, Jemal A. Trends in prostate cancer incidence rates and prevalence of prostate-specific antigen screening by socioeconomic status and regions in the US, 2004-2013. J Urol 2017;199:676-682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28965781.

47. Maurice MJ, Kim SP, Abouassaly R. Current status of prostate cancer diagnosis and management in the United States. JAMA Oncol 2016;2:1505-1507. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27356204.

48. Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-specific antigen screening after 2012 US Preventive Services Task Force recommendations. JAMA 2015;314:2077-2079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26575066.

49. Zavaski ME, Meyer CP, Sammon JD, et al. Differences in prostate-specific antigen testing among urologists and primary care physicians following the 2012 USPSTF recommendations. JAMA Intern Med 2016;176:546-547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26857148.

50. Magnani CJ, Li K, Seto T, et al. PSA testing use and prostate cancer diagnostic stage after the 2012 U.S. Preventive Services Task Force guideline changes. J Natl Compr Canc Netw 2019;17:795-803. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31319390.

51. Becker DJ, Rude T, Walter D, et al. The Association of Veterans' PSA screening rates with changes in USPSTF recommendations. J Natl Cancer Inst 2021;113:626-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32797212.

52. Weiner AB, Matulewicz RS, Eggener SE, Schaeffer EM. Increasing incidence of metastatic prostate cancer in the United States (2004-2013). Prostate Cancer Prostatic Dis 2016;19:395-397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27431496.

53. Hu JC, Nguyen P, Mao J, et al. Increase in prostate cancer distant metastases at diagnosis in the United States. JAMA Oncol 2017;3:705-707. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28033446.

54. Jemal A, Culp MB, Ma J, et al. Prostate cancer incidence 5 years after US Preventive Services Task Force recommendations against screening. J Natl Cancer Inst 2020;113:64-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32432713.

55. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA 2018;319:1901-1913. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29801017.

56. Fenton JJ, Weyrich MS, Durbin S, et al. Prostate-specific antigen-based screening for prostate cancer: Evidence report and systematic review for the US Preventive Services Task Force. JAMA 2018;319:1914-1931. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29801018.

57. Leapman MS, Wang R, Park H, et al. Changes in prostate-specific antigen testing relative to the revised US Preventive Services Task Force recommendation on prostate cancer screening. JAMA Oncol 2022;8:41-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34762100.

58. Gosselaar C, Roobol MJ, Roemeling S, et al. Screening for prostate cancer at low PSA range: the impact of digital rectal examination on tumor incidence and tumor characteristics. Prostate 2007;67:154-161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17044079.

59. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994;151:1283-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7512659.

60. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. JAMA 1993;270:948-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7688438.

61. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 2017;197:S200-S207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28012755.

62. Flanigan RC, Catalona WJ, Richie JP, et al. Accuracy of digital rectal examination and transrectal ultrasonography in localizing prostate cancer. J Urol 1994;152:1506-1509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7523707.

63. Schroder FH, van der Maas P, Beemsterboer P, et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 1998;90:1817-1823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9839522.

64. Arsov C, Albers P, Herkommer K, et al. A randomized trial of risk-adapted screening for prostate cancer in young men-Results of the first screening round of the PROBASE trial. Int J Cancer 2022;150:1861-1869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35076933.

65. Okotie OT, Roehl KA, Han M, et al. Characteristics of prostate cancer detected by digital rectal examination only. Urology 2007;70:1117-1120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18158030.

66. Hattangadi JA, Chen MH, D'Amico AV. Early detection of high-grade prostate cancer using digital rectal examination (DRE) in men with a prostate-specific antigen level of <2.5 ng/mL and the risk of death. BJU international 2012;110:1636-1641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22757982.

67. Halpern JA, Shoag JE, Mittal S, et al. Prognostic significance of digital rectal examination and prostate specific antigen in the prostate, lung, colorectal and ovarian (PLCO) cancer screening arm. J Urol 2017;197:363-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27569432.

68. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006;98:529-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16622122.

69. Halpern JA, Oromendia C, Shoag JE, et al. Utility of digital rectal examination (DRE) as an adjunct to prostate specific antigen (PSA) in the detection of clinically significant prostate cancer. J Urol 2018;199:947-953. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29061540.

70. Gosselaar C, Roobol MJ, Roemeling S, Schroder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol 2008;54:581-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18423977.

71. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-1328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19297566.

72. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22417251.

73. Heijnsdijk EA, Wever EM, Auvinen A, et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012;367:595-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22894572.

74. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027-2035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25108889.

75. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: New insights from the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2015;68:885-890. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25791513.

76. Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol 2019;76:43-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30824296.

77. Roobol MJ, Kranse R, Bangma CH, et al. Screening for prostate cancer: results of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2013;64:530-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23759326.

78. Bokhorst LP, Bangma CH, van Leenders GJ, et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2014;65:329-336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23954085.

79. Kilpelainen TP, Tammela TL, Malila N, et al. Prostate cancer mortality in the Finnish randomized screening trial. J Natl Cancer Inst 2013;105:719-725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23479454.

80. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725-732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20598634.

81. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. Eur Urol 2015;68:354-360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25556937.

82. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013;64:703-709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721957.

83. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22228146.

84. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123:592-599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27911486.

85. Pinsky PF, Blacka A, Kramer BS, et al. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Clin Trials 2010;7:303-311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20571134.

86. Shoag JE, Mittal S, Hu JC. Reevaluating PSA testing rates in the PLCO trial. N Engl J Med 2016;374:1795-1796. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27144870.

87. Andriole GL. Update of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Recent Results Cancer Res 2014;202:53-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24531777.

88. Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med 2017;167:449-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28869989.

89. Crawford ED, Grubb R, 3rd, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol 2011;29:355-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21041707.

90. Bach PB, Vickers AJ. Do the data support the comorbidity hypothesis for the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial results? J Clin Oncol 2011;29:e387. Available at: http://jco.ascopubs.org/content/29/13/e387.short.

91. Martin RM, Donovan JL, Turner EL, et al. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: The CAP randomized clinical trial. JAMA 2018;319:883-895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29509864.

92. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19297565.

93. Carlsson S, Assel M, Ulmert D, et al. Screening for prostate cancer starting at age 50-54 years. A population-based cohort study. Eur Urol 2017;71:46-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27084245.

94. Howard K, Barratt A, Mann GJ, Patel MI. A model of prostate-specific antigen screening outcomes for low- to high-risk men: information to support informed choices. Arch Intern Med 2009;169:1603-1610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19786680.

95. Lilja H, Cronin AM, Dahlin A, et al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. Cancer 2011;117:1210-1219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20960520.

96. Weight CJ, Narayan VM, Smith D, et al. The effects of population-based prostate-specific antigen screening beginning at age 40. Urology 2017;110:127-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28842211.

97. Vickers AJ, Ulmert D, Sjoberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ 2013;346:f2023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23596126.

98. Preston MA, Batista JL, Wilson KM, et al. Baseline prostate-specific antigen levels in midlife predict lethal prostate cancer. J Clin Oncol 2016;34:2705-2711. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27298404.

99. Kovac E, Carlsson SV, Lilja H, et al. Association of baseline prostate-specific antigen level with long-term diagnosis of clinically significant prostate cancer among patients aged 55 to 60 years: A secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. JAMA Netw Open 2020;3:e1919284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31940039.

100. van Leeuwen PJ, Roobol MJ, Kranse R, et al. Towards an optimal interval for prostate cancer screening. Eur Urol 2012;61:171-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21840117.

101. Roobol MJ, Roobol DW, Schroder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology 2005;65:343-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15708050.

102. Ulmert D, Cronin AM, Bjork T, et al. Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: a case-control study. BMC Med 2008;6:6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18279502.

103. Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. BMJ 2010;341:c4521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20843935.

104. Vertosick EA, Haggstrom C, Sjoberg DD, et al. Prespecified 4-kallikrein marker model at age 50 or 60 for early detection of lethal prostate cancer in a large population based cohort of asymptomatic men followed for 20 years. J Urol 2020;204:281-288. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32125228.

105. Preston MA, Gerke T, Carlsson SV, et al. Baseline prostate-specific antigen level in midlife and aggressive prostate cancer in black men. Eur Urol 2019;75:399-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30237027.

106. Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. BMJ 2014;348:g2296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24682399.

107. Heijnsdijk EAM, Gulati R, Tsodikov A, et al. Lifetime benefits and harms of prostate-specific antigen-based risk-stratified screening for prostate cancer. J Natl Cancer Inst 2020;112:1013-1020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32067047.

108. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen--based prostate cancer screening strategies: model estimates of potential benefits and harms. Ann Intern Med

2013;158:145-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23381039.

109. Nyame YA, Gulati R, Heijnsdijk EAM, et al. The impact of intensifying prostate cancer screening in Black men: A model-based analysis. J Natl Cancer Inst 2021;113:1336-1342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33963850.

110. Sun L, Caire AA, Robertson CN, et al. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. J Urol 2009;182:2242-2248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19758616.

111. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. J Clin Oncol 2011;29:235-241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135285.

112. Clark R, Vesprini D, Narod SA. The effect of age on prostate cancer survival. Cancers (Basel) 2022;14:4149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36077685.

113. Scosyrev E, Messing EM, Mohile S, et al. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer 2012;118:3062-3070. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22006014.

114. Pettersson A, Robinson D, Garmo H, et al. Age at diagnosis and prostate cancer treatment and prognosis: a population-based cohort study. Ann Oncol 2018;29:377-385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161337.

115. Schaeffer EM, Carter HB, Kettermann A, et al. Prostate specific antigen testing among the elderly--when to stop? J Urol 2009;181:1606-1614; discussion 1613-1604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19246059.

116. Bratt O. Hereditary prostate cancer: clinical aspects. J Urol 2002;168:906-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12187189.

117. Carter BS, Beaty TH, Steinberg GD, et al. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A 1992;89:3367-3371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1565627.

118. Chen YC, Page JH, Chen R, Giovannucci E. Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. Prostate 2008;68:1582-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18646000.

119. Grill S, Fallah M, Leach RJ, et al. Incorporation of detailed family history from the Swedish Family Cancer Database into the PCPT risk calculator. J Urol 2015;193:460-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25242395.

120. Mahal BA, Chen YW, Muralidhar V, et al. Racial disparities in prostate cancer outcome among prostate-specific antigen screening eligible populations in the United States. Ann Oncol 2017;28:1098-1104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28453693.

121. Randazzo M, Muller A, Carlsson S, et al. A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). BJU Int 2016;117:576-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26332304.

122. Shenoy D, Packianathan S, Chen AM, Vijayakumar S. Do African-American men need separate prostate cancer screening guidelines? BMC Urol 2016;16:19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27165293.

123. Chamie K, DeVere White RW, Lee D, et al. Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. Cancer 2008;113:2464-2470. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18666213.

124. Ansbaugh N, Shannon J, Mori M, et al. Agent Orange as a risk factor for high-grade prostate cancer. Cancer 2013;119:2399-2404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23670242.

125. Jansson F, Drevin L, Frisell T, et al. Concordance of non-low-risk disease among pairs of brothers with prostate cancer. J Clin Oncol 2018;36:1847-1852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29652556.

126. Bratt O, Drevin L, Akre O, et al. Family history and probability of postate cancer, differentiated by risk category: a nationwide population-based study. J Natl Cancer Inst 2016;108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27400876.

127. Plonis J, Nakazawa-Miklasevica M, Malevskis A, et al. Survival rates of familial and sporadic prostate cancer patients. Exp Oncol 2015;37:154-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26112946.

128. Raheem OA, Cohen SA, Parsons JK, et al. A family history of lethal prostate cancer and risk of aggressive prostate cancer in patients undergoing radical prostatectomy. Sci Rep 2015;5:10544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26112134.

129. Barber L, Gerke T, Markt SC, et al. Family history of breast or prostate cancer and prostate cancer risk. Clin Cancer Res 2018;24:5910-5917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30082473.

130. Ren ZJ, Cao DH, Zhang Q, et al. First-degree family history of breast cancer is associated with prostate cancer risk: a systematic review and meta-analysis. BMC Cancer 2019;19:871. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31477094.

131. Tangen CM, Goodman PJ, Till C, et al. Biases in recommendations for and acceptance of prostate biopsy significantly affect assessment of prostate cancer risk factors: Results from two large randomized clinical trials. J Clin Oncol 2016;34:4338-4344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27998216.

132. Welch HG, Brawley OW. Scrutiny-dependent cancer and self-fulfilling risk factors. Ann Intern Med 2018;168:143-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29297002.

133. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27433846.

134. Ewing CM, Ray AM, Lange EM, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366:141-149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22236224.

135. Xu J, Lange EM, Lu L, et al. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet 2013;132:5-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23064873.

136. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, et al. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Ann Oncol 2015;26:756-761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25595936.

137. Darst BF, Hughley R, Pfennig A, et al. A rare germline HOXB13 variant contributes to risk of prostate cancer in men of african ancestry. Eur Urol 2022;81:458-462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35031163.

138. Giri VN, Knudsen KE, Kelly WK, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020;38:2798-2811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32516092.

139. Bancroft EK, Page EC, Brook MN, et al. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. Lancet Oncol 2021;22:1618-1631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34678156.

140. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol

2012;30:4409-4415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23091106.

141. Haraldsdottir S, Hampel H, Wei L, et al. Prostate cancer incidence in males with Lynch syndrome. Genet Med 2014;16:553-557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24434690.

142. Raymond VM, Mukherjee B, Wang F, et al. Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 2013;31:1713-1718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23530095.

143. Rosty C, Walsh MD, Lindor NM, et al. High prevalence of mismatch repair deficiency in prostate cancers diagnosed in mismatch repair gene mutation carriers from the colon cancer family registry. Fam Cancer 2014;13:573-582. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25117503.

144. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:437-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24425144.

145. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in lynch syndrome. J Natl Cancer Inst 2012;104:1363-1372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22933731.

146. Yang X, Leslie G, Doroszuk A, et al. Cancer risks associated with germline PALB2 pathogenic variants: An international study of 524 families. J Clin Oncol 2020;38:674-685. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31841383.

147. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33:2345-2352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26014290.

148. Maxwell KN, Cheng HH, Powers J, et al. Inherited TP53 variants and risk of prostate cancer. Eur Urol 2022;81:243-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34863587.

149. Nelson HD, Fu R, Goddard K, et al. U.S. Preventive Services Task Force evidence syntheses, formerly systematic evidence reviews. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24432435.

150. John EM, Miron A, Gong G, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 2007;298:2869-2876. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18159056.

151. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst 1999;91:1310-1316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10433620.

152. Agalliu I, Gern R, Leanza S, Burk RD. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res 2009;15:1112-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188187.

153. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 1994;343:692-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7907678.

154. Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010;16:2115-2121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20215531.

155. Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res 2004;10:2918-2921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15131025.

156. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106:1697-1701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22516946.

157. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004;22:735-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14966099.

158. Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94:1358-1365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12237281.

159. Tulinius H, Olafsdottir GH, Sigvaldason H, et al. The effect of a single BRCA2 mutation on cancer in Iceland. J Med Genet 2002;39:457-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12114473.

160. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16141007.

161. Mersch J, Jackson MA, Park M, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 2015;121:269-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25224030.

162. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 2012;11:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22187320.

163. Li S, Silvestri V, Leslie G, et al. Cancer risks associated with BRCA1 and BRCA2 pathogenic variants. J Clin Oncol 2022;40:1529-1541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35077220.

164. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-1757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23569316.

165. Mitra A, Fisher C, Foster CS, et al. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. Br J Cancer 2008;98:502-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182994.

166. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740-747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27989354.

167. Narod SA, Neuhausen S, Vichodez G, et al. Rapid progression of prostate cancer in men with a BRCA2 mutation. Br J Cancer 2008;99:371-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18577985.

168. Thorne H, Willems AJ, Niedermayr E, et al. Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. Cancer Prev Res (Phila) 2011;4:1002-1010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21733824.

169. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007;99:929-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17565157.

170. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: Evidence for prostate-specific antigen screening in BRCA2 mutation carriers. Eur Urol 2019;76:831-842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31537406.

171. Odedina FT, Akinremi TO, Chinegwundoh F, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer 2009;4 Suppl 1:S2. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19208207.

172. Fletcher SA, Marchese M, Cole AP, et al. Geographic distribution of racial differences in prostate cancer mortality. JAMA Netw Open 2020;3:e201839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32232449.

173. Lillard JW, Jr., Moses KA, Mahal BA, George DJ. Racial disparities in Black men with prostate cancer: A literature review. Cancer 2022;128:3787-3795. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36066378.

174. Wang M, Chi G, Bodovski Y, et al. Temporal and spatial trends and determinants of aggressive prostate cancer among Black and White men with prostate cancer. Cancer Causes Control 2020;31:63-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31732913.

175. Mahal BA, Berman RA, Taplin ME, Huang FW. Prostate cancer-specific mortality across gleason scores in Black vs nonblack men. JAMA 2018;320:2479-2481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30561471.

176. Carthon B, Sibold HC, Blee S, Pentz RD. Prostate cancer: Community education and disparities in diagnosis and treatment. Oncologist 2021;26:537-548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33683758.

177. Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. Cancer 2017;123:2312-2319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28436011.

178. Moses KA, Orom H, Brasel A, et al. Racial/Ethnic Disparity in Treatment for Prostate Cancer: Does Cancer Severity Matter? Urology 2017;99:76-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27667157.

179. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. J Urol 2010;183:1792-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20299055.

180. Robbins HA, Engels EA, Pfeiffer RM, Shiels MS. Age at cancer diagnosis for blacks compared with whites in the United States. J Natl Cancer Inst 2015;107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25638255.

181. Karami S, Young HA, Henson DE. Earlier age at diagnosis: another dimension in cancer disparity? Cancer Detect Prev 2007;31:29-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17303347.

182. Metcalfe C, Evans S, Ibrahim F, et al. Pathways to diagnosis for Black men and White men found to have prostate cancer: the PROCESS cohort study. Br J Cancer 2008;99:1040-1045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18797456.

183. Barocas DA, Grubb R, 3rd, Black A, et al. Association between race and follow-up diagnostic care after a positive prostate cancer screening test in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer 2013;119:2223-2229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23559420.

184. Han Y, Rand KA, Hazelett DJ, et al. Prostate cancer susceptibility in men of African ancestry at 8q24. J Natl Cancer Inst 2016;108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26823525.

185. Mahal BA, Aizer AA, Ziehr DR, et al. Trends in disparate treatment of African American men with localized prostate cancer across National Comprehensive Cancer Network risk groups. Urology 2014;84:386-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24975710.

186. Yamoah K, Johnson MH, Choeurng V, et al. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. J Clin Oncol 2015;33:2789-2796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26195723.

187. Zhang H, Messing EM, Travis LB, et al. Age and racial differences among PSA-detected (AJCC stage T1cN0M0) prostate cancer in the U.S.:

a population-based study of 70,345 men. Front Oncol 2013;3:312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24392353.

188. Vince RA, Jr., Jiang R, Bank M, et al. Evaluation of social determinants of health and prostate cancer outcomes among Black and white patients: A systematic review and meta-analysis. JAMA Netw Open 2023;6:e2250416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36630135.

189. Schumacher FR, Basourakos SP, Lewicki PJ, et al. Race and genetic alterations in prostate cancer. JCO Precis Oncol 2021;5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34746633.

190. Riviere P, Luterstein E, Kumar A, et al. Survival of African American and non-Hispanic white men with prostate cancer in an equal-access health care system. Cancer 2020;126:1683-1690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31984482.

191. Sutton SS, Crawford ED, Moul JW, et al. Determining optimal prostate-specific antigen thresholds to identify an increased 4-year risk of prostate cancer development: an analysis within the Veterans Affairs Health Care System. World J Urol 2016;34:1107-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26753559.

192. Basourakos SP, Gulati R, Vince RA, Jr., et al. Harm-to-benefit of three decades of prostate cancer screening in Black men. NEJM Evid 2022;1. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35721307.

193. Schroder FH, Roobol-Bouts M, Vis AN, et al. Prostate-specific antigen-based early detection of prostate cancer--validation of screening without rectal examination. Urology 2001;57:83-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11164149.

194. Ankerst DP, Hoefler J, Bock S, et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. Urology 2014;83:1362-1367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24862395.

195. Foley RW, Maweni RM, Gorman L, et al. European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators significantly outperform the Prostate Cancer Prevention Trial (PCPT) 2.0 in the prediction of prostate cancer: a multi-institutional study. BJU Int 2016;118:706-713. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26833820.

196. Louie KS, Seigneurin A, Cathcart P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Ann Oncol 2015;26:848-864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25403590.

197. Nam RK, Kattan MW, Chin JL, et al. Prospective multi-institutional study evaluating the performance of prostate cancer risk calculators. J Clin Oncol 2011;29:2959-2964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21690464.

198. Nam RK, Toi A, Klotz LH, et al. Assessing individual risk for prostate cancer. J Clin Oncol 2007;25:3582-3588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17704405.

199. Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol 2010;57:79-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19733959.

200. Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculators. Eur Urol 2019;75:310-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30082150.

201. Glass AS, Cary KC, Cooperberg MR. Risk-based prostate cancer screening: who and how? Curr Urol Rep 2013;14:192-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23532499.

202. Kuru TH, Roethke MC, Seidenader J, et al. Critical evaluation of magnetic resonance imaging targeted, transrectal ultrasound guided transperineal fusion biopsy for detection of prostate cancer. J Urol

2013;190:1380-1386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23608676.

203. Lamb BW, Tan WS, Rehman A, et al. Is prebiopsy MRI good enough to avoid prostate biopsy? A cohort study over a 1-year period. Clin Genitourin Cancer 2015;13:512-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26231912.

204. Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014;66:22-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24666839.

205. Serrao EM, Barrett T, Wadhwa K, et al. Investigating the ability of multiparametric MRI to exclude significant prostate cancer prior to transperineal biopsy. Can Urol Assoc J 2015;9:E853-858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26788234.

206. Tonttila PP, Lantto J, Paakko E, et al. Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol 2016;69:419-425. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26033153.

207. Weaver JK, Kim EH, Vetter JM, et al. Presence of magnetic resonance imaging suspicious lesion predicts Gleason 7 or greater prostate cancer in biopsy-naive patients. Urology 2016;88:119-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26545849.

208. Wysock JS, Mendhiratta N, Zattoni F, et al. Predictive value of negative 3T multiparametric prostate MRI on 12 core biopsy results. BJU Int 2016;118:515-520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26800439.

209. Goldberg H, Ahmad AE, Chandrasekar T, et al. Comparison of magnetic resonance imaging and transrectal ultrasound informed prostate biopsy for prostate cancer diagnosis in biopsy naive men: A systematic review and meta-analysis. J Urol 2020;203:1085-1093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31609177.

210. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28110982.

211. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767-1777. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29552975.

212. Boesen L, Norgaard N, Logager V, Thomsen HS. Clinical outcome following low suspicion multiparametric prostate magnetic resonance imaging or benign magnetic resonance imaging guided biopsy to detect prostate cancer. J Urol 2017;198:310-315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28235549.

213. Hansen NL, Barrett T, Kesch C, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naive men with suspicion of prostate cancer. BJU Int 2018;122:40-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29024425.

214. Lu AJ, Syed JS, Nguyen KA, et al. Negative multiparametric magnetic resonance imaging of the prostate predicts absence of clinically significant prostate cancer on 12-core template prostate biopsy. Urology 2017;105:118-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28322902.

215. Simmons LAM, Kanthabalan A, Arya M, et al. The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy. Br J Cancer 2017;116:1159-1165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28350785.

216. van Leeuwen PJ, Hayen A, Thompson JE, et al. A multiparametric magnetic resonance imaging-based risk model to determine the risk of

significant prostate cancer prior to biopsy. BJU Int 2017;120:774-781. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28207981.

217. Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100-109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30470502.

218. van der Leest M, Cornel E, Israel B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naive men with elevated prostate-specific antigen: A large prospective multicenter clinical study. Eur Urol 2019;75:570-578. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30477981.

219. Eklund M, Jaderling F, Discacciati A, et al. MRI-targeted or standard biopsy in prostate cancer screening. N Engl J Med 2021;385:908-920. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34237810.

220. Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917-928. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130814.

221. Klotz L, Chin J, Black PC, et al. Comparison of multiparametric magnetic resonance imaging-targeted biopsy with systematic transrectal ultrasonography biopsy for biopsy-naive men at risk for prostate cancer: A phase 3 randomized clinical trial. JAMA Oncol 2021;7:534-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33538782.

222. Hugosson J, Mansson M, Wallstrom J, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. N Engl J Med 2022;387:2126-2137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36477032.

223. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25626035.

224. Mendhiratta N, Rosenkrantz AB, Meng X, et al. Magnetic resonance imaging-ultrasound fusion targeted prostate biopsy in a consecutive cohort of men with no previous biopsy: reduction of over detection through improved risk stratification. J Urol 2015;194:1601-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26100327.

225. Meng X, Rosenkrantz AB, Mendhiratta N, et al. Relationship between prebiopsy multiparametric magnetic resonance imaging (MRI), biopsy indication, and MRI-ultrasound fusion-targeted prostate biopsy outcomes. Eur Urol 2016;69:512-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26112001.

226. Elkhoury FF, Felker ER, Kwan L, et al. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naive: The prospective assessment of image registration in the diagnosis of prostate cancer (PAIREDCAP) study. JAMA Surg 2019;154:811-818. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31188412.

227. Filson CP, Natarajan S, Margolis DJ, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: The role of systematic and targeted biopsies. Cancer 2016;122:884-892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26749141.

228. Porpiglia F, Manfredi M, Mele F, et al. Diagnostic pathway with multiparametric magnetic resonance imaging versus standard pathway: results from a randomized prospective study in biopsy-naive patients with suspected prostate cancer. Eur Urol 2017;72:282-288. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27574821.

229. Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev 2019;4:CD012663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31022301.

230. Elwenspoek MMC, Sheppard AL, McInnes MDF, et al. Comparison of multiparametric magnetic resonance imaging and targeted biopsy with

systematic biopsy alone for the diagnosis of prostate cancer: A systematic review and meta-analysis. JAMA Netw Open 2019;2:e198427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31390032.

231. Sathianathen NJ, Omer A, Harriss E, et al. Negative predictive value of multiparametric magnetic resonance imaging in the detection of clinically significant prostate cancer in the prostate imaging reporting and data system era: A systematic review and meta-analysis. Eur Urol 2020;78:402-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32444265.

232. Lo G, Burton KR, Haider MA, et al. Negative predictive value of prostate multiparametric magnetic resonance imaging among men with negative prostate biopsy and elevated prostate specific antigen: A clinical outcome retrospective cohort study. J Urol 2019;202:1159-1165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31188731.

233. Richenberg J, Logager V, Panebianco V, et al. The primacy of multiparametric MRI in men with suspected prostate cancer. Eur Radiol 2019;29:6940-6952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31172275.

234. Westphalen AC, McCulloch CE, Anaokar JM, et al. Variability of the positive predictive value of PI-RADS for prostate MRI across 26 centers: Experience of the society of abdominal radiology prostate cancer disease-focused panel. Radiology 2020;296:76-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32315265.

235. Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver reproducibility of the PI-RADS version 2 lexicon: A multicenter study of six experienced prostate radiologists. Radiology 2016;280:793-804. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27035179.

236. Sonn GA, Fan RE, Ghanouni P, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. Eur Urol Focus 2017;5:592-599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29226826.

237. Borofsky S, George AK, Gaur S, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2017;286:152877. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29053402.

238. Pagniez MA, Kasivisvanathan V, Puech P, et al. Predictive factors of missed clinically significant prostate cancers in men with negative magnetic resonance imaging: A systematic review and meta-analysis. J Urol 2020;204:24-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31967522.

239. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol 2016;196:1613-1618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27320841.

240. Auprich M, Augustin H, Budaus L, et al. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy. BJU Int 2012;109:1627-1635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21939492.

241. Boegemann M, Stephan C, Cammann H, et al. The percentage of prostate-specific antigen (PSA) isoform [-2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged ≤65 years. BJU Int 2016;117:72-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25818705.

242. Bruzzese D, Mazzarella C, Ferro M, et al. Prostate health index vs percent free prostate-specific antigen for prostate cancer detection in men with "gray" prostate-specific antigen levels at first biopsy: systematic review and meta-analysis. Transl Res 2014;164:444-451. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25035153.

243. De Luca S, Passera R, Bollito E, et al. Comparison of prostate cancer gene 3 score, prostate health index and percentage free prostate-specific

antigen for differentiating histological inflammation from prostate cancer and other non-neoplastic alterations of the prostate at initial biopsy. Anticancer Res 2014;34:7159-7165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25503144.

244. De Luca S, Passera R, Fiori C, et al. Prostate health index and prostate cancer gene 3 score but not percent-free Prostate Specific Antigen have a predictive role in differentiating histological prostatitis from PCa and other nonneoplastic lesions (BPH and HG-PIN) at repeat biopsy. Urol Oncol 2015;33:424.e17-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26162485.

245. Ferro M, Bruzzese D, Perdona S, et al. Prostate Health Index (PHI) and Prostate Cancer Antigen 3 (PCA3) significantly improve prostate cancer detection at initial biopsy in a total PSA range of 2-10 ng/ml. PLoS One 2013;8:e67687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23861782.

246. Nordstrom T, Vickers A, Assel M, et al. Comparison between the four-kallikrein panel and Prostate Health Index for predicting prostate cancer. Eur Urol 2015;68:139-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25151013.

247. Perdona S, Bruzzese D, Ferro M, et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate 2013;73:227-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22821756.

248. Porpiglia F, Russo F, Manfredi M, et al. The roles of multiparametric magnetic resonance imaging, PCA3 and prostate health index-which is the best predictor of prostate cancer after a negative biopsy? J Urol 2014;192:60-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24518780.

249. Russo GI, Regis F, Castelli T, et al. A systematic review and meta-analysis of the diagnostic accuracy of Prostate Health Index and 4-kallikrein panel score in predicting overall and high-grade prostate cancer. Clin Genitourin Cancer 2017;15:429-439.e1. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28111174.

250. Scattoni V, Lazzeri M, Lughezzani G, et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. J Urol 2013;190:496-501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23466239.

251. Vedder MM, de Bekker-Grob EW, Lilja HG, et al. The added value of percentage of free to total prostate-specific antigen, PCA3, and a kallikrein panel to the ERSPC risk calculator for prostate cancer in prescreened men. Eur Urol 2014;66:1109-1115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25168616.

252. Wysock JS, Becher E, Persily J, et al. Concordance and performance of 4Kscore and SelectMDx for informing decision to perform prostate biopsy and detection of prostate cancer. Urology 2020;141:119-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32294481.

253. Gnanapragasam VJ, Burling K, George A, et al. The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant prostate cancers in a repeat biopsy population. Sci Rep 2016;6:35364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27748407.

254. Punnen S, Nahar B, Soodana-Prakash N, et al. Optimizing patient's selection for prostate biopsy: A single institution experience with multi-parametric MRI and the 4Kscore test for the detection of aggressive prostate cancer. PLoS One 2018;13:e0201384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30092002.

255. Mannaerts CK, Gayet M, Verbeek JF, et al. Prostate cancer risk assessment in biopsy-naive patients: The rotterdam prostate cancer risk calculator in multiparametric magnetic resonance imaging-transrectal ultrasound (TRUS) fusion biopsy and systematic TRUS biopsy. Eur Urol Oncol 2018;1:109-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31100233.

256. Falagario UG, Martini A, Wajswol E, et al. Avoiding unnecessary magnetic resonance imaging (MRI) and biopsies: Negative and positive predictive value of MRi according to prostate-specific antigen density, 4Kscore and risk calculators. Eur Urol Oncol 2020;3:700-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31548130.

257. Partin AW, Brawer MK, Subong EN, et al. Prospective evaluation of percent free-PSA and complexed-PSA for early detection of prostate cancer. Prostate Cancer Prostatic Dis 1998;1:197-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12496895.

258. Veneziano S, Pavlica P, Querze R, et al. Correlation between prostate-specific antigen and prostate volume, evaluated by transrectal ultrasonography: usefulness in diagnosis of prostate cancer. Eur Urol 1990;18:112-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1699766.

259. Benson MC, Whang IS, Pantuck A, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol 1992;147:815-816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1371554.

260. Lujan M, Paez A, Llanes L, et al. Prostate specific antigen density. Is there a role for this parameter when screening for prostate cancer? Prostate Cancer Prostatic Dis 2001;4:146-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12497032.

261. Allan RW, Sanderson H, Epstein JI. Correlation of minute (0.5 MM or less) focus of prostate adenocarcinoma on needle biopsy with radical prostatectomy specimen: role of prostate specific antigen density. J Urol 2003;170:370-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12853777.

262. Radwan MH, Yan Y, Luly JR, et al. Prostate-specific antigen density predicts adverse pathology and increased risk of biochemical failure. Urology 2007;69:1121-1127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17572199.

263. Gittelman MC, Hertzman B, Bailen J, et al. PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. J Urol 2013;190:64-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23416644.

264. Bradley LA, Palomaki GE, Gutman S, et al. Comparative effectiveness review: prostate cancer antigen 3 testing for the diagnosis and management of prostate cancer. J Urol 2013;190:389-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23545099.

265. Auprich M, Bjartell A, Chun FK, et al. Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. Eur Urol 2011;60:1045-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21871709.

266. Aubin SM, Reid J, Sarno MJ, et al. PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. J Urol 2010;184:1947-1952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20850153.

267. Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol 2014;32:4066-4072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25385735.

268. Filella X, Gimenez N. Evaluation of [-2] proPSA and Prostate Health Index (phi) for the detection of prostate cancer: a systematic review and meta-analysis. Clin Chem Lab Med 2013;51:729-739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23154423.

269. Lazzeri M, Haese A, Abrate A, et al. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU Int 2013;112:313-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23826841.

270. Loeb S. Prostate cancer: Prostate Health Index--improving screening in men with family history. Nat Rev Urol 2013;10:497-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23938945.

271. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0

to 10.0 ng/ml prostate specific antigen range. J Urol 2011;185:1650-1655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21419439.

272. de la Calle C, Patil D, Wei JT, et al. Multicenter evaluation of the Prostate Health Index to detect aggressive prostate cancer in biopsy naive men. J Urol 2015;194:65-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25636659.

273. Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int 2017;120:61-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27743489.

274. Tosoian JJ, Druskin SC, Andreas D, et al. Prostate Health Index density improves detection of clinically significant prostate cancer. BJU Int 2017;120:793-798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28058757.

275. Tosoian JJ, Druskin SC, Andreas D, et al. Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice. Prostate Cancer Prostatic Dis 2017;20:228-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28117387.

276. White J, Shenoy BV, Tutrone RF, et al. Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a large group urology practice setting. Prostate Cancer Prostatic Dis 2017;21:78-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29158509.

277. Ehdaie B, Carlsson S. Reply to 'Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a large group urology practice setting'. Prostate Cancer Prostatic Dis 2018;21:446-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29858593.

278. Vickers A, Cronin A, Roobol M, et al. Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. J Clin Oncol 2010;28:2493-2498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20421547.

279. Vickers AJ, Gupta A, Savage CJ, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. Cancer Epidemiol Biomarkers Prev 2011;20:255-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21148123.

280. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol 2015;68:464-470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25454615.

281. Bryant RJ, Sjoberg DD, Vickers AJ, et al. Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. J Natl Cancer Inst 2015;107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25863334.

282. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore test reduces prostate biopsy rates in community and academic urology practices. Rev Urol 2015;17:231-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26839521.

283. Stewart GD, Van Neste L, Delvenne P, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. J Urol 2013;189:1110-1116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22999998.

284. Partin AW, Van Neste L, Klein EA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. J Urol 2014;192:1081-1087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24747657.

285. Chevli KK, Duff M, Walter P, et al. Urinary PCA3 as a predictor of prostate cancer in a cohort of 3,073 men undergoing initial prostate biopsy. J Urol 2014;191:1743-1748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24333241.

286. McKiernan J, Donovan MJ, O'Neill V, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial

biopsy. JAMA Oncol 2016;2:882-889. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27032035.

287. McKiernan J, Donovan MJ, Margolis E, et al. A prospective adaptive utility trial to validate performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer in patients with prostate-specific antigen 2-10ng/ml at initial biopsy. Eur Urol 2018;74:731-738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30237023.

288. Tutrone R, Donovan MJ, Torkler P, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10 ng/mL. Prostate Cancer Prostatic Dis 2020;23:607-614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32382078.

289. Leyten GH, Hessels D, Smit FP, et al. Identification of a candidate gene panel for the early diagnosis of prostate cancer. Clin Cancer Res 2015;21:3061-3070. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25788493.

290. Rizzardi AE, Rosener NK, Koopmeiners JS, et al. Evaluation of protein biomarkers of prostate cancer aggressiveness. BMC Cancer 2014;14:244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24708576.

291. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of high-grade prostate cancer using a urinary molecular biomarker-based risk score. Eur Urol 2016;70:740-748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27108162.

292. Hendriks RJ, van der Leest MMG, Dijkstra S, et al. A urinary biomarker-based risk score correlates with multiparametric MRI for prostate cancer detection. Prostate 2017;77:1401-1407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28853167.

293. Haese A, Trooskens G, Steyaert S, et al. Multicenter optimization and validation of a 2-gene mRNA urine test for detection of clinically significant prostate cancer before initial prostate biopsy. J Urol 2019;202:256-263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31026217.

294. Klein EA, Chait A, Hafron JM, et al. The single-parameter, structure-based isopsa assay demonstrates improved diagnostic accuracy for detection of any prostate cancer and high-grade prostate cancer compared to a concentration-based assay of total prostate-specific antigen: A preliminary report. Eur Urol 2017;72:942-949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28396176.

295. Klein EA, Partin A, Lotan Y, et al. Clinical validation of IsoPSA, a single parameter, structure-focused assay for improved detection of prostate cancer: A prospective, multicenter study. Urol Oncol 2022;40:408.e9-408.e18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35840465.

296. Scovell JM, Hettel D, Abouassaly R, et al. isoPSA reduces provider recommendations for biopsy and magnetic resonance imaging in men with total prostate specific antigen ≥4 ng/ml: a real-world observational clinical utility study. Urol Pract 2022;9:173-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37145695.

297. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG plus PCA3 for individualized prostate cancer risk assessment. Eur Urol 2016;70:45-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25985884.

298. Rubin MA, Maher CA, Chinnaiyan AM. Common gene rearrangements in prostate cancer. J Clin Oncol 2011;29:3659-3668. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21859993.

299. Perner S, Mosquera JM, Demichelis F, et al. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. Am J Surg Pathol 2007;31:882-888. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17527075.

300. Young A, Palanisamy N, Siddiqui J, et al. Correlation of urine TMPRSS2:ERG and PCA3 to ERG+ and total prostate cancer burden. Am J Clin Pathol 2012;138:685-696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23086769.

301. Tosoian JJ, Trock BJ, Morgan TM, et al. Use of the MyProstateScore test to rule out clinically significant cancer: Validation of a straightforward clinical testing approach. J Urol 2021;205:732-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080150.

302. Wang WW, Sorokin I, Aleksic I, et al. Expression of small noncoding RNAs in urinary exosomes classifies prostate cancer into indolent and aggressive disease. J Urol 2020;204:466-475. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191585.

303. Strom P, Nordstrom T, Aly M, et al. The Stockholm-3 model for prostate cancer detection: Algorithm update, biomarker contribution, and reflex test potential. Eur Urol 2018;74:204-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29331214.

304. Nordstrom T, Discacciati A, Bergman M, et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. Lancet Oncol 2021;22:1240-1249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34391509.

305. Presti JC, Jr., O'Dowd GJ, Miller MC, et al. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol 2003;169:125-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12478119.

306. Ukimura O, Coleman JA, de la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol 2013;63:214-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23021971.

307. Sivaraman A, Sanchez-Salas R, Barret E, et al. Transperineal template-guided mapping biopsy of the prostate. Int J Urol 2015;22:146-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25421717.

308. Xiang J, Yan H, Li J, et al. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol 2019;17:31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30760274.

309. Roberts MJ, Macdonald A, Ranasinghe S, et al. Transrectal versus transperineal prostate biopsy under intravenous anaesthesia: a clinical, microbiological and cost analysis of 2048 cases over 11 years at a tertiary institution. Prostate Cancer Prostatic Dis 2021;24:169-176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32759972.

310. Stangl-Kremser J, Ramaswamy A, Hu JC. Transperineal vs. transrectal biopsy to reduce postinterventional sepsis. Curr Opin Urol 2023;33:193-199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36861767.

311. Jacewicz M, Gunzel K, Rud E, et al. Antibiotic prophylaxis versus no antibiotic prophylaxis in transperineal prostate biopsies (NORAPP): a randomised, open-label, non-inferiority trial. Lancet Infect Dis 2022;22:1465-1471. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35839791.

312. Mian BM, Feustel PJ, Aziz A, et al. Complications Following Transrectal and Transperineal Prostate Biopsy: Results of the ProBE-PC Randomized Clinical Trial. J Urol 2024;211:205-213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37976319.

313. Rastinehad AR, Turkbey B, Salami SS, et al. Improving detection of clinically significant prostate cancer: MRI/TRUS fusion-guided prostate biopsy. J Urol 2013;191:1749-1754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24333515.

314. Robertson NL, Emberton M, Moore CM. MRI-targeted prostate biopsy: a review of technique and results. Nature reviews. Urology 2013;10:589-597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24061532.

315. Puech P, Rouviere O, Renard-Penna R, et al. Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy--prospective

multicenter study. Radiology 2013;268:461-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23579051.

316. Wegelin O, Exterkate L, van der Leest M, et al. The FUTURE trial: A multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. Eur Urol 2019;75:582-590. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30522912.

317. Ploussard G, Borgmann H, Briganti A, et al. Positive pre-biopsy MRI: are systematic biopsies still useful in addition to targeted biopsies? World J Urol 2019;37:243-251. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29967944.

318. Hoeks CM, Schouten MG, Bomers JG, et al. Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers. Eur Urol 2012;62:902-909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22325447.

319. Portalez D, Mozer P, Cornud F, et al. Validation of the European Society of Urogenital Radiology scoring system for prostate cancer diagnosis on multiparametric magnetic resonance imaging in a cohort of repeat biopsy patients. Eur Urol 2012;62:986-996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22819387.

320. Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65:809-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23523537.

321. Vourganti S, Rastinehad A, Yerram NK, et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. J Urol 2012;188:2152-2157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23083875.

322. Roethke M, Anastasiadis AG, Lichy M, et al. MRI-guided prostate biopsy detects clinically significant cancer: analysis of a cohort of 100 patients after previous negative TRUS biopsy. World J Urol 2012;30:213-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21512807.

323. Sciarra A, Panebianco V, Ciccariello M, et al. Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy. Clin Cancer Res 2010;16:1875-1883. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20197480.

324. Anastasiadis AG, Lichy MP, Nagele U, et al. MRI-guided biopsy of the prostate increases diagnostic performance in men with elevated or increasing PSA levels after previous negative TRUS biopsies. Eur Urol 2006;50:738-748; discussion 748-749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16630688.

325. Rais-Bahrami S, Siddiqui MM, Turkbey B, et al. Utility of multiparametric magnetic resonance imaging suspicion levels for detecting prostate cancer. J Urol 2013;190:1721-1727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23727310.

326. Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25480312.

327. Klotz L, Lughezzani G, Maffei D, et al. Comparison of micro-ultrasound and multiparametric magnetic resonance imaging for prostate cancer: A multicenter, prospective analysis. Can Urol Assoc J 2021;15:E11-E16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701437.

328. Stone NN, Crawford ED, Skouteris VM, et al. The ratio of the number of biopsy specimens to prostate volume (biopsy density) greater than 1.5 improves the prostate cancer detection rate in men undergoing

transperineal biopsy of the prostate. J Urol 2019;202:264-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30835628.

329. Nelson AW, Harvey RC, Parker RA, et al. Repeat prostate biopsy strategies after initial negative biopsy: meta-regression comparing cancer detection of transperineal, transrectal saturation and MRI guided biopsy. PLoS One 2013;8:e57480. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23460864.

330. Abdollah F, Novara G, Briganti A, et al. Trans-rectal versus trans-perineal saturation rebiopsy of the prostate: is there a difference in cancer detection rate? Urology 2011;77:921-925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21131034.

331. Acher P, Dooldeniya M. Prostate biopsy: will transperineal replace transrectal? BJU Int 2013;112:533-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23924418.

332. Grummet JP, Weerakoon M, Huang S, et al. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? BJU Int 2014;114:384-388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24612341.

333. Pepe P, Aragona F. Morbidity after transperineal prostate biopsy in 3000 patients undergoing 12 vs 18 vs more than 24 needle cores. Urology 2013;81:1142-1146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23726443.

334. Vyas L, Acher P, Challacombe B, et al. Indications, results and safety profile of transperineal sector biopsies of the prostate: a single centre experience of 634 cases. BJU Int 2013;114:32-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24053629.

335. Murphy DG, Weerakoon M, Grummet J. Is zero sepsis alone enough to justify transperineal prostate biopsy? BJU Int 2014;114:3-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24964181.

336. Taira AV, Merrick GS, Galbreath RW, et al. Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting. Prostate Cancer Prostatic Dis 2010;13:71-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19786982.

337. Merrick GS, Gutman S, Andreini H, et al. Prostate cancer distribution in patients diagnosed by transperineal template-guided saturation biopsy. Eur Urol 2007;52:715-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17337114.

338. Walz J, Graefen M, Chun FK, et al. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. Eur Urol 2006;50:498-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16631303.

339. Zaytoun OM, Moussa AS, Gao T, et al. Office based transrectal saturation biopsy improves prostate cancer detection compared to extended biopsy in the repeat biopsy population. J Urol 2011;186:850-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21788047.

340. Liss MA, Ehdaie B, Loeb S, et al. An update of the American Urological Association white paper on the prevention and treatment of the more common complications related to prostate biopsy. J Urol 2017;198:329-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28363690.

341. Begier E, Rosenthal NA, Gurtman A, et al. Epidemiology of invasive Escherichia coli infection and antibiotic resistance status among patients treated in US hospitals: 2009-2016. Clin Infect Dis 2021;73:565-574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33420788.

342. Lightner DJ, Wymer K, Sanchez J, Kavoussi L. Best practice statement on urologic procedures and antimicrobial prophylaxis. J Urol 2020;203:351-356. Available at: https://pubmed.ncbi.nlm.nih.gov/31441676/.

343. Feliciano J, Teper E, Ferrandino M, et al. The incidence of fluoroquinolone resistant infections after prostate biopsy--are fluoroquinolones still effective prophylaxis? J Urol 2008;179:952-955;

discussion 955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207185.

344. Zaytoun OM, Vargo EH, Rajan R, et al. Emergence of fluoroquinolone-resistant Escherichia coli as cause of postprostate biopsy infection: implications for prophylaxis and treatment. Urology 2011;77:1035-1041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21420152.

345. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm. Accessed September 14, 2023.

346. Tops SCM, Kolwijck E, Koldewijn EL, et al. Rectal culture-based versus empirical antibiotic prophylaxis to prevent infectious complications in men undergoing transrectal prostate biopsy: A randomized, nonblinded multicenter trial. Clin Infect Dis 2023;76:1188-1196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36419331.

347. Djavan B, Waldert M, Zlotta A, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol 2001;166:856-860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11490233.

348. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64:876-892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23787356.

349. Collins GN, Lloyd SN, Hehir M, McKelvie GB. Multiple transrectal ultrasound-guided prostatic biopsies--true morbidity and patient acceptance. Br J Urol 1993;71:460-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8499991.

350. Stirling BN, Shockley KF, Carothers GG, Maatman TJ. Comparison of local anesthesia techniques during transrectal ultrasound-guided biopsies. Urology 2002;60:89-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12100930.

351. Hergan L, Kashefi C, Parsons JK. Local anesthetic reduces pain associated with transrectal ultrasound-guided prostate biopsy: a meta-analysis. Urology 2007;69:520-525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17382157.

352. Lunacek A, Mrstik C, Simon J, et al. Combination of lidocaine suppository and periprostatic nerve block during transrectal prostate biopsy: a prospective randomized trial. Int J Urol 2014;21:1126-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24974854.

353. Jindal T, Mukherjee S, Sinha RK, et al. Transrectal ultrasonography (TRUS)-guided pelvic plexus block to reduce pain during prostate biopsy: a randomised controlled trial. BJU Int 2015;115:892-896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25046032.

354. Lv Z, Jiang H, Hu X, et al. Efficacy and safety of periprostatic nerve block combined with perineal subcutaneous anaesthesia and intrarectal lidocaine gel in transrectal ultrasound guided transperineal prostate biopsy: A Prospective Randomised Controlled Trial. Prostate Cancer Prostatic Dis 2020;23:74-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31160805.

355. Leibovici D, Zisman A, Siegel YI, et al. Local anesthesia for prostate biopsy by periprostatic lidocaine injection: a double-blind placebo controlled study. J Urol 2002;167:563-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11792919.

356. Schröder FH, Roobol MJ. PSA screening decision-making aid for patients, general practitioners and urologists: Societe Internationale D'Urologie; 2014. Available at: http://www.siu-urology.org/themes/web/assets/files/society/psa_testing_brochure.pdf.

357. Testing for Prostate Cancer. American Cancer Society; 2020. Available at: https://www.cancer.org/content/dam/cancer-org/cancer-control/en/booklets-flyers/testing-for-prostate-cancer-handout.pdf. Accessed September 14, 2023.

358. Riikonen JM, Guyatt GH, Kilpeläinen TP, et al. Decision aids for prostate cancer screening choice: A systematic review and meta-analysis.

JAMA Intern Med 2019;179:1072-1082. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31233091.

359. Kovi J, Jackson MA, Heshmat MY. Ductal spread in prostatic carcinoma. Cancer 1985;56:1566-1573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4027893.

360. Dinerman BF, Khani F, Golan R, et al. Population-based study of the incidence and survival for intraductal carcinoma of the prostate. Urol Oncol 2017;35:673.e9-673.e14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28919182.

361. Kimura K, Tsuzuki T, Kato M, et al. Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. Prostate 2014;74:680-687. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24481730.

362. Cohen RJ, McNeal JE, Baillie T. Patterns of differentiation and proliferation in intraductal carcinoma of the prostate: significance for cancer progression. Prostate 2000;43:11-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10725861.

363. McNeal JE, Yemoto CE. Significance of demonstrable vascular space invasion for the progression of prostatic adenocarcinoma. Am J Surg Pathol 1996;20:1351-1360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8898839.

364. Miyai K, Divatia MK, Shen SS, et al. Clinicopathological analysis of intraductal proliferative lesions of prostate: intraductal carcinoma of prostate, high-grade prostatic intraepithelial neoplasia, and atypical cribriform lesion. Hum Pathol 2014;45:1572-1581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24842280.

365. O'Brien C, True LD, Higano CS, et al. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. Am J Clin Pathol 2010;133:654-661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20231619.

366. Rubin MA, de La Taille A, Bagiella E, et al. Cribriform carcinoma of the prostate and cribriform prostatic intraepithelial neoplasia: incidence and clinical implications. Am J Surg Pathol 1998;22:840-848. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9669346.

367. Wilcox G, Soh S, Chakraborty S, et al. Patterns of high-grade prostatic intraepithelial neoplasia associated with clinically aggressive prostate cancer. Hum Pathol 1998;29:1119-1123. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9781651.

368. Van der Kwast T, Al Daoud N, Collette L, et al. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. Eur J Cancer 2012;48:1318-1325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22405699.

369. Saeter T, Vlatkovic L, Waaler G, et al. Intraductal carcinoma of the prostate on diagnostic needle biopsy predicts prostate cancer mortality: A population-based study. Prostate 2017;77:859-865. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28240424.

370. Trinh VQ, Sirois J, Benzerdjeb N, et al. The impact of intraductal carcinoma of the prostate on the site and timing of recurrence and cancer-specific survival. Prostate 2018;78:697-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29603326.

371. Porter LH, Lawrence MG, Ilic D, et al. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. Eur Urol 2017;72:492-495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28342640.

372. Shah RB, Magi-Galluzzi C, Han B, Zhou M. Atypical cribriform lesions of the prostate: relationship to prostatic carcinoma and implication for diagnosis in prostate biopsies. Am J Surg Pathol 2010;34:470-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20182345.

373. Hickman RA, Yu H, Li J, et al. Atypical intraductal cribriform proliferations of the prostate exhibit similar molecular and clinicopathologic characteristics as intraductal carcinoma of the prostate. Am J Surg Pathol

2017;41:550-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28009609.

374. Shah RB, Nguyen JK, Przybycin CG, et al. Atypical intraductal proliferation detected in prostate needle biopsy is a marker of unsampled intraductal carcinoma and other adverse pathological features: a prospective clinicopathological study of 62 cases with emphasis on pathological outcomes. Histopathology 2019;75:346-353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31012493.

375. Morais CL, Han JS, Gordetsky J, et al. Utility of PTEN and ERG immunostaining for distinguishing high-grade PIN from intraductal carcinoma of the prostate on needle biopsy. Am J Surg Pathol 2015;39:169-178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25517949.

376. Bostwick DG, Cheng L. Precursors of prostate cancer. Histopathology 2012;60:4-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22212075.

377. Herawi M, Kahane H, Cavallo C, Epstein JI. Risk of prostate cancer on first re-biopsy within 1 year following a diagnosis of high grade prostatic intraepithelial neoplasia is related to the number of cores sampled. J Urol 2006;175:121-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16406886.

378. O'Dowd G J, Miller MC, Orozco R, Veltri RW. Analysis of repeated biopsy results within 1 year after a noncancer diagnosis. Urology 2000;55:553-559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10736500.

379. Taneja SS, Morton R, Barnette G, et al. Prostate cancer diagnosis among men with isolated high-grade intraepithelial neoplasia enrolled onto a 3-year prospective phase III clinical trial of oral toremifene. J Clin Oncol 2013;31:523-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23295793.

380. Thompson IM, Jr., Leach R. Prostate cancer and prostatic intraepithelial neoplasia: true, true, and unrelated? J Clin Oncol 2013;31:515-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23295801.

381. Ericson KJ, Wenger HC, Rosen AM, et al. Prostate cancer detection following diagnosis of atypical small acinar proliferation. Can J Urol 2017;24:8714-8720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28436357.

382. Dorin RP, Wiener S, Harris CD, Wagner JR. Prostate atypia: does repeat biopsy detect clinically significant prostate cancer? Prostate 2015;75:673-678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25597982.

383. Chan TY, Epstein JI. Follow-up of atypical prostate needle biopsies suspicious for cancer. Urology 1999;53:351-355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9933053.

384. Mian BM, Naya Y, Okihara K, et al. Predictors of cancer in repeat extended multisite prostate biopsy in men with previous negative extended multisite biopsy. Urology 2002;60:836-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12429311.

385. Wiener S, Haddock P, Cusano J, et al. Incidence of clinically significant prostate cancer after a diagnosis of atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, or benign tissue. Urology 2017;110:161-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28888752.

386. Leone A, Rotker K, Butler C, et al. Atypical small acinar proliferation: Repeat biopsy and detection of high grade prostate cancer. Prostate Cancer 2015;2015:810159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26451257.

387. Ynalvez LA, Kosarek CD, Kerr PS, et al. Atypical small acinar proliferation at index prostate biopsy: rethinking the re-biopsy paradigm. Int Urol Nephrol 2018;50:1-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29064003.

388. Kawa SM, Stroomberg HV, Larsen SB, et al. A nationwide analysis of risk of prostate cancer diagnosis and mortality following an initial negative transrectal ultrasound biopsy with long-term followup. J Urol 2022;208:100-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35212571.

389. Grivas N, Lardas M, Espinos EL, et al. Prostate cancer detection percentages of repeat biopsy in patients with positive multiparametric magnetic resonance imaging (Prostate Imaging Reporting and Data System/Likert 3-5) and negative initial biopsy. A mini systematic review. Eur Urol 2022;82:452-457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35985901.

390. Morote J, Schwartzmann I, Celma A, et al. The current recommendation for the management of isolated high-grade prostatic intraepithelial neoplasia. BJU Int 2022;129:627-633. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34375498.

391. Kotb AF, Spaner S, Crump T, Hyndman ME. The role of mpMRI and PSA density in patients with an initial negative prostatic biopsy. World J Urol 2018;36:2021-2025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29808301.