CE Review

The Case for Tailored Prostate Cancer Screening: An NCCN Perspective

Michelle L. McDonald, MD, and J. Kellogg Parsons, MD, MHS

Abstract

A preponderance of clinical evidence supports a significant public health benefit for screening and early detection of prostate cancer in selected men. The challenge lies in maximizing early diagnosis of potentially aggressive but curable disease while minimizing diagnosis and treatment of indolent disease. A tailored approach to population screening in appropriately counseled men, using an evidence-based strategy with judicious prostate-specific antigen (PSA) testing, will reduce prostate-cancer mortality yet limit overdetection of clinically insignificant disease. Use of newer biomarkers that increase specificity for prostate cancer detection, including percentage of free PSA, 4Kscore, prostate health index, prostate cancer antigen 3, and multiparametric MRI may be considered under certain circumstances. (J Natl Compr Canc Netw 2015;13:1576–1583)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the rationale for tailoring prostate cancer early detection toward younger populations
- Explain how biomarkers and imaging studies might improve the specificity of prostate cancer detection

From the Department of Urology, UC San Diego Health System, La Jolla, California.

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Correspondence: J. Kellogg Parsons, MD, MHS, Department of Urology, UC San Diego Health System, 3855 Health Sciences Drive #0987, La Jolla, CA 92093-0987. E-mail: k0parsons@mail.ucsd.edu

EDITOR

Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*

Ms. Green has disclosed that she has no relevant financial relationships.

CE AUTHORS

Deborah J. Moonan, RN, BSN, Director, Continuing Education, has disclosed that she has no relevant financial relationships.

Ann Gianola, MA, Manager, Continuing Education Accreditation & Program Operations, has disclosed that she has no relevant financial relationships.

Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships.

Rashmi Kumar, PhD, Senior Manager, Clinical Content, has disclosed that she has no relevant financial relationships.

Deborah A. Freedman-Cass, PhD, Oncology Scientist/Senior Medical Writer, has disclosed that she has no relevant financial relationships.

Overview

Prostate cancer remains the most commonly diagnosed noncutaneous cancer and the second leading cause of cancer death among men in the United States. In 2015, approximately 220,800 men will be diagnosed with and 27,540 will die of prostate cancer.[1] Since the early 1990s,[1] prostate cancer mortality has decreased 45%. Although potentially due in part to lead time bias after earlier detection through widespread use of prostate-specific antigen (PSA) testing, this trend has also largely been attributed to the treatment of screen-detected tumors.[2–4] Randomized trials have since confirmed the efficacy of PSA population screening to diminish prostate cancer mortality (Table 1).

Nevertheless, aggressive screening, diagnosis, and treatment of prostate cancer has generated debate regarding overdetection.[5] Overdetection is the diagnosis of screen-detected indolent prostate cancer that, left untreated, would otherwise not provoke symptoms or diminish overall or prostate cancer–specific survival. Overtreatment of screen-detected indolent cancers with surgery and radiation may expose patients to substantial risks of urinary incontinence, erectile dysfunction, and proctitis.

The NCCN Prostate Cancer Early Detection Guidelines Panel recognizes that not all men diagnosed with prostate cancer require treatment. They acknowledge that maximizing the early detection of prostate cancer will increase the detection of both indolent and aggressive cancers among informed men who have elected to participate in a screening program.[6] To decrease prostate cancer mortality, yet mitigate against the potential morbidities of overdetection and overtreatment, the panel has recommended a tailored approach to prostate cancer screening emphasizing judicious application of evidence-based principles.[6]

Weighing the Evidence: Population-Based PSA Screening Trials

In 2012, the US Preventive Services Task Force (USPSTF) concluded from the available evidence that the potential harms of PSA testing outweigh its potential benefits, and issued a "D" grade for PSA testing, recommending against population-based screening for prostate cancer.[7]

However, results of 2 of 3 randomized controlled trials of PSA screening—the European Randomized Study of Screening for Prostate Cancer (ERSPC)[8] and the Göteborg screening trial[9]—suggested a substantial public health benefit to screening in the form of reduced prostate cancer mortality. Moreover, although the third trial, the prostate arm of the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, showed no benefit to screening, the PLCO could not assess the benefit of PSA-based screening on prostate cancer mortality because of excessive screening in the control arm.

The ERSPC, initiated in 1991 among 7 different European countries, randomized 162,388 men aged 55 to 69 years to a screening or control arm.[8] Men were screened every 2 to 4 years with a PSA test. After 13 years of follow-up, the rate ratio of prostate cancer mortality in the screened arm was 21% (95% CI, 0.69–0.91), equivalent to 1 prostate cancer death averted per 781 men screened, or 1 per 27 additional prostate cancers detected.[10] Potential shortcomings of the ERSPC include lack of a significant effect of screening on all-cause mortality, overreliance on secondary analyses adjusting for noncompliance, and unbalanced treatment differences between study arms.[11,12]

The Göteborg screening trial randomized 20,000 men aged 50 to 64 years to biannual PSA-based screening or a control condition until age 69 years.[9] At a median follow-up of 14 years, a 44% risk reduction in prostate cancer-related deaths was seen in the screening arm. Notably, half of the prostate cancers detected in the screening arm were not immediately treated, suggesting a survival benefit even when early detection is combined with selective treatment.

The PLCO trial was performed in 10 centers across the United States from 1993 to 2001.[13,14] A total of 76,685 men aged 55 to 74 years were randomized to screening or usual care (control arm). Screened men were offered an annual PSA test for 6 years and a digital rectal examination (DRE) for 4 years. Although no difference in prostate cancer mortality was seen between the groups at a median follow-up 13 years, there was significant noncompliance in the control arm, with a compliance rate of 52% per year versus 85% in the screening arm; 74% of men in the control arm were screened at least once. Poor compliance in the control arm would have driven differences between the arms toward the null. In addition, the PLCO trial also had very low biopsy rates among men with elevated PSA levels: 40% in the first year and 30% by the third year.[15] Thus, the PLCO arm could not effectively test

Table 1 Randomized Controlled PSA-Based Screening Trials and Subanalyses

Study, Year	Study Population	Study Sample	Intervention	Median Length of Follow-Up, y	PCa Death Reduction	Limitations	Comments
ERSPC,[8,10] 2009	7 European countries 1991–2003	162,388 men aged 55–69 y	Randomized to PSA screening every 2–4 y or control Prostate biopsy most often when PSA level >3 ng/mL	9	Yes RRR=20% NNT=48	Median age of men was >60 y Long screening interval (largely q4y) Inconsistencies in screening interval and biopsy threshold	NNT assumes all men diagnosed are treated, therefore was rephrased in subsequent reports
				11	Yes RRR=21% NND=37		
				13	Yes RRR=21% NND=27		
Göteborg,[9] 2010	Goteborg, Sweden, 1944	20,000 men aged 50–64 y	Randomized to biannual PSA screening or control until age 69 y Prostate biopsy when PSA level >2.5–3.0 ng/mL	14	Yes RRR=44% NND=12	60% of men born between 1930–1939 previously included in overall ERSPC results	Half of the men with PCa detected in screened arm were not immediately treated Contamination rate estimated at 3% Not independent from larger ERSPC trial
Rotterdam,[59,60] 2014	Rotterdam, Netherlands, 1993–2010	34,833 men aged 55–69 y	Randomized to PSA screening q4y until age 75 y Biopsy when PSA level ≥3–4 ng/mL	13	Yes RRR=32% When corrected for nonattendance and contamination, RRR=51%	Extrapolation of PSA contamination data Use of questionnaire to assess reason for PSA testing in those without PCa	
PLCO,[13,14] 2009	10 US centers, 1993–2001	76,685 men aged 55–74 y	Randomized to screening with annual PSA testing for 6 y & DRE for 4 y or usual care (control) Biopsy when PSA level ≥4 ng/mL	13	No	Significant noncompliance in control arm: 74% were screened at least once Low biopsy rates in men with elevated PSA levels	Not a trial of screening vs no screening, but rather annual screening vs ad hoc screening
Leob et al,[23] 2011	10 US centers, 1993–2001	73,378 men aged 55–75 y who filled out comorbidity questionnaire before study entry	See PLCO	10	Yes, when results analyzed by comorbidity status, RRR=44%	Possible methodological errors in analysis	Suggests screening is more useful among men in good health

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; DRE, digital rectal examination; NND, number needed to detect; NNT, number needed to treat; PCa, prostate cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; RRR, relative risk reduction.

whether a screening intervention reduced prostate cancer mortality compared with a control condition.

Collectively, the level I evidence from these trials—2 observing robust overall benefits, 1 suggesting a significant benefit in a subgroup analysis—supports PSA screening to reduce prostate cancer mortality.

Shifting the Screening Strategy

The 2 extremes of a PSA-screening strategy—pursuit of unrefined, unconstrained PSA testing versus blanket cessation of all testing—both fail to acknowledge the biologic heterogeneity of prostate cancer.[16] Screen-detected prostate cancers constitute a spectrum of disease,

ranging from indolent (most of the cases diagnosed) to highly aggressive (which usually merit treatment with surgery or radiation even in older patients).[17]

Charting an even-handed, evidence-based path between the 2 extremes involves tailoring early detection efforts toward screening of younger populations and developing more stringent biopsy criteria.

Informed and Shared Decision-Making

Screening should be offered only to informed patients who have agreed to participate in an early detection program. Shared decision-making is a process in which physicians and patients collaborate to make decisions. The process requires informed patients.[18] The responsibility of the physician is to help the patient understand the nature of the decision by providing evidence-based data and streamlined information.[19,20] Patients should be counseled that the purpose of screening is to detect aggressive prostate cancers that are potentially curable, but they should also be advised that, in the process of detecting these cancers, indolent cancers may also be identified.[19] Men should be counseled that the detection of indolent cancer does not equate to treatment, or at least immediate treatment, and that management must be individualized.[19,21] The discussion should also include the potential direct harms of screening,[18] which include false-positive PSA tests, potential additional unnecessary tests (ie, prostate biopsy), anxiety, diminished quality of life, risks of prostate biopsy, and risks of treatment.[22–24]

Risk Factors and Life Expectancy

Older age, African American race, and family history of prostate cancer are associated with increased risk of prostate cancer diagnosis and death. No PSA-based screening trial to date, or subgroup model of a screening trial, has definitively assessed the potential benefits of differential screening in higher-risk populations, and no population-based data demonstrate that selective screening of African Americans or men with a family history leads to improved cancer-specific or overall survival. PSA value is a stronger predictor for prostate cancer than race or positive family history.[25] Therefore, although these risk factors may be considered in the decision to participate in screening, the intensity of screening, and/or in the interpretation of screening test results, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection do not offer separate screening recommendations for African Americans or positive family history.[6]

The prevalence of overdetection depends in large part on life expectancy at the time of diagnosis. Men with limited life expectancies secondary to comorbid conditions and/or advanced age are the least likely to benefit from screening.[26,27] Life expectancy estimation is therefore an important consideration in the decision to participate in screening. PSA testing should therefore only be offered to men with a 10-or-more-year life expectancy. Physicians tend to overestimate life expectancy and underestimate comorbidity[28]; resources such as the Social Security Administration tables for life expectancy estimation may aid in decision-making.[29]

Digital Rectal Examination

The role of DRE as a diagnostic tool for prostate cancer is uncertain in the modern era. DRE has poor sensitivity, limited specificity, and high interobserver variability.[30,31] In the Prostate Cancer Prevention Trial, Thompson et al[32] concluded that DRE added little value to screening, with an absolute difference of only 0.02 in the area under the curve for detecting prostate cancer compared with PSA alone.

On the other hand, men in the ERSPC with a serum PSA level greater than 3 ng/mL and abnormal DRE findings were more likely to be diagnosed with prostate cancer than those with a PSA level greater than 3 ng/mL alone.[33] DRE potentially may also help identify aggressive cancers in patients with lower (<2.5 ng/mL) PSA values.[34]

Therefore, although DRE should not be used as a stand-alone screening test, it should be performed in men with an elevated PSA level, and may be considered as a baseline test in all men undergoing PSA screening, because it may potentially identify higher-risk cancer in men with lower PSA values.[6]

Age at Which to Initiate PSA Testing

The ERSPC and Göteborg trials observed a reduction in prostate cancer mortality in men who initiated screening at age 50 to 55 years, with the strongest evidence supporting testing beginning at

age 55 years. One hypothesis for the more robust mortality improvements observed in the Göteborg compared with the ERSPC trials were the median ages at study entry: 56 and 60 years, respectively. Despite these data, only 24% of men between the ages of 50 and 54 years are typically screened in the United States, and screening rates peak in men aged 70 to 74 years.[35]

Data suggest that screening men aged 40 to 49 years confers only modest improvements in 10-year prostate cancer mortality.[36] However, some observational data suggest that there may be utility in testing men aged 40 to 55 years to aid in future risk stratification. A cohort study of Swedish men determined that a baseline PSA in early mid-life (45–55 years) identifies men at risk for metastases several decades later.[37]

Based on these data, particularly the Göteborg study, it is reasonable to target a younger population of healthy men for PSA screening, with an age for screening initiation of 45 years.

Age at Which to Discontinue PSA Testing

Determining the age at which to discontinue screening in men with previously normal PSA values is a contentious issue. Approximately 50% of all prostate cancer screening occurs in older men (70–79 years), suggesting that most overdetection occurs in older men who are the least likely to develop clinically significant disease during their lifespan.[35] The ERSPC observed no benefit to screening men beyond age 70 years, whereas another study using prostate cancer microsimulation models predicted that decreasing the screening termination age from 74 years to 69 years would lead to a 50% reduction in the probability of overdetection.[38] The same study also assessed screening up to age 74 years while simultaneously increasing the PSA threshold for biopsy with increasing age, and determined that this strategy reduced overdiagnosis by one-third. Still, data from a surgical cohort of more than 4,500 men from the PSA screening era suggested that, compared with younger men, men older than 70 years had a significantly higher risk of adverse pathology and similar risks of biochemical recurrence, metastases, and prostate cancer–specific death.[39]

The NCCN Prostate Cancer Early Detection Panel acknowledges the difficulty in identifying a stopping age for screening, and that its panelists did not agree on this issue. At this time, the panel recommends screening up to age 75 years, with consideration given to offering screening to extremely healthy men older than 75 years using tools such as the Social Security Administration actuarial tables for life expectancy (category 2B recommendation).[29]

Tailored Screening Frequency

Previous evidence-based guidelines have recommended annual screening.[40–42] However, there are now data from randomized controlled trials to suggest that annual screening provides no additional survival benefit compared with screening at 2-year intervals. The NCCN Prostate Cancer Early Detection Panel acknowledges the difficulty in identifying a suitable interval for screening. However, although there is limited consensus, screening intervals may be tailored to PSA and age, with longer intervals used for younger men with lower PSA levels, because PSA value predicts future risk of clinically significant disease in younger men.[43]

Age 45 to 75 Years

In men with a PSA level of less than 1 ng/mL who have elected to undergo screening, PSA testing should be performed at 2- to 4-year intervals; for those with a PSA level of 1.0 ng/mL or greater and less than 3.0 ng/mL, testing should be performed at 1- to 2-year intervals.[40,43–46] For this age group, a PSA level greater than 1.0 ng/mL corresponds with the greater than 75th percentile for the population and is associated with increased risks of incident cancer and incident clinically significant cancer.[44]

Age Older Than 75 Years

In this age group, screening may potentially be offered to very healthy men with a relatively high likelihood of clinically significant cancer, because the potential for overdetection is high and very few men will benefit.[9,14,38,47]

Considerations for Biopsy

Prostate biopsy may be considered for those men with a PSA level greater than 3.0 ng/mL with or without abnormal DRE results.[40] In men older than 75 years, consideration may be given to increasing the PSA threshold to greater than 4 ng/mL.[38,48] Otherwise, age-adjusted PSA cut points are not routinely recommended. Transrectal ultrasound-guided biopsy should

be performed in an extended pattern with a minimum of 12 cores obtained—sextant (6) and lateral peripheral zone (6)—that should incorporate palpable nodules and/or suspicious ultrasound images. Anteriorly directed biopsy is not recommended for a routine initial biopsy, but may be considered in the setting of a repeat biopsy. Other approaches that may be considered, particularly for repeat biopsy, include saturation techniques and transperineal templates.[6]

Biomarkers

Although currently not indicated as first-line screening tests, for patients and physicians who wish to further define the probability of biopsy-detectable cancer, consideration may be given to newer biomarker tests that increase the specificity of prostate cancer detection, including percent free PSA (%free PSA),[49] the prostate health index (PHI),[50] prostate cancer antigen 3 (PCA3),[51] and the 4-kallikrein (4Kscore) panel (Table 2).[52] These tests may inform the decision to perform biopsy as a result of improved specificity for the detection of clinically significant prostate cancer compared with total PSA. The PHI incorporates the [-2] isoform of proPSA into the formula PHI = ([-2] proPSA/freePSA) x √PSA and, in a multicenter study, was noted to have double the sensitivity of total or free PSA for cancer detection in men with a PSA level between 2 and 10 ng/dL.[53] The 4Kscore panel includes total PSA, free PSA,

Table 2 Additional Tests for the Early Detection of PCa in Setting of Elevated PSA

	Test Name	Sample	Year of FDA Approval	Measures	Comments
No prior biopsy	phi	Blood	2012	Variants of PSA PHI = ([-2] proPSA/freePSA) x √PSA	Recommended in men with PSA level between 3 and 10 ng/mL PHI >35 suspicious for PCa
	4Kscore panel	Blood	N/A	4 kallikrein markers: total PSA, free PSA, intact PSA, hK2	Provides a probability score, 0%–100%, of clinically significant PCa on biopsy
Negative prior biopsy	phi	Blood	2012	Variants of PSA PHI = ([-2] proPSA/freePSA) x √PSA	Recommended in men with PSA level between 3 and 10 ng/mL PHI >35 suspicious for PCa
	4Kscore panel	Blood	N/A	4 kallikrein markers: total PSA, free PSA, intact PSA, hK2	Provides a probability score, 0%–100%, of clinically significant PCa on biopsy
	%free PSA	Blood	1998	Unbound PSA as a ratio of total PSA	Recommended in men with PSA level between 4 and 10 ng/mL %free PSA <10% suspicious for PCa
	PCA3	Urine	2012	Prostate tissue–specific RNA	Approved in setting of negative biopsy in men aged >50 y PCA3 level >35 suspicious for PCa
	MRI	N/A	N/A	Scoring systems for suspicion of identified lesions[a]	Suspicious lesions can be used as targets for biopsy
	Confirm-MDX[b]	Prostate biopsy tissue	N/A	Measures epigenetic field effect from hypermethylation of DNA	Predicts probability of undiagnosed cancer

Abbreviations: 4Kscore, 4-kallikrein; %free PSA, percentage of free prostate-specific antigen; √PSA, square root of prostate specific antigen; hK2, human kallikrein 2; N/A, not applicable; PCa, prostate cancer; PCA3, prostate cancer antigen 3; phi, prostate health index; PIRADS, prostate imaging reporting and data system; proPSA, pro-prostate specific antigen; PSA, prostate-specific antigen.
[a]The PIRADS system is based on probability of clinically significant cancer and ranges from PIRADS 1 (ie, very low, clinically significant cancer is highly unlikely to be present) to PIRADS 5 (ie, very high, clinically significant cancer is highly likely to be present)
[b]The NCCN Prostate Cancer Early Detection Panel has not issued evidence-based recommendations regarding this assay.

intact PSA, and human kallikrein 2 (hK2); several studies have confirmed its accuracy in the detection of clinically significant cancer (Gleason score ≥7) and its potential to reduce the number of unnecessary biopsies.[52,54]

The PHI and 4Kscore[54] tests are potentially informative during initial screening in men who have never undergone biopsy; PHI, 4Kscore, %free PSA, and urinary PCA3 are robust in selecting for repeat biopsy in those patients who have undergone at least one prior negative biopsy.[51,55]

MRI

Increasing interest is being shown in the role of multiparametric MRI in prostate cancer diagnosis. Recent evidence suggests a benefit of MRI-targeted prostate biopsy compared with standard transrectal ultrasound-guided biopsy in the detection of clinically significant cancer.[56] However, to date no definitive data show that MRI informs the decision to perform an initial prostate biopsy. Therefore, with respect to prostate cancer diagnosis, consideration of MRI is currently recommended only in patients with a prior negative biopsy.[6]

Tissue Assays

At least one commercial assay exists that uses tissue from a prior negative biopsy to predict the probability of prostate cancer diagnosis on repeat biopsy. This assay measures an epigenetic field effect based on DNA hypermethylation in paraffin-embedded tissue.[57,58] The NCCN Prostate Cancer Early Detection Panel does not recommend its use at this time, and it remains unclear whether this assay informs the decision to perform repeat biopsy after a prior negative biopsy in the context of other available biomarkers (ie, PHI, 4Kscore, %free PSA, and PCA3).[6]

Conclusions

Level 1 evidence indicates that prostate cancer screening reduces prostate cancer–specific mortality. A judicious, tailored approach to population screening using PSA testing every 1 to 4 years in appropriately counseled men ages 50 to 75 years would substantially reduce prostate cancer mortality, yet limit overdetection of clinically insignificant disease. Although prostate biopsy may be considered in appropriately selected patients with PSA levels less than 3 ng/mL, newer biomarkers, including 4Kscore, PHI, %free PSA, and urinary PCA3, and multiparametric prostate MRI, may improve specificity for prostate cancer detection and thus inform the decision to perform prostate biopsy.

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Posttest Questions

1. Shared decision-making will result in more informed patients. Which of the following should clinicians discuss with their patients before recommending a prostate cancer early detection program?
   A. Risks of prostate biopsy
   B. Risks of treatment
   C. False-positive PSA tests
   D. All of the above
   E. Both B and C
2. True or False: PSA value is a stronger predictor for prostate cancer than race or positive family history.
3. For men between the ages of 45–75 years who have elected to undergo screening and with a PSA ≥1.0 ng/mL and <3.0 ng/mL, PSA testing should be performed at:
   A. Yearly
   B. 1 to 2 year intervals
   C. 2 to 4 year intervals
   D. There are no formal recommendations