### NCCN Guidelines Version 1.2014
Prostate Cancer Early Detection Panel Members

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### NCCN Guidelines Panel Disclosures

- **Medical oncology**
- § **Radiotherapy/Radiation oncology**
- ¶ **Surgical oncology**
- ○ **Urology**
- ≈ **Internal Medicine**
- ≠ **Pathology**
- & **Epidemiology**
- † † **Biostatistician**
- ¥ **Patient advocacy**
- * **Writing committee member**

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# NCCN Prostate Cancer Early Detection Panel Members

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

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

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

See NCCN Categories of Evidence and Consensus.
Summary of changes in the 1.2014 version of the NCCN Guidelines for Prostate Cancer Early Detection from the 2.2012 version include:

The guidelines have been extensively revised.

Major changes include:

- The algorithm has been shortened and streamlined

**PROSD-2**

- The ages to start testing have been stratified

**PROSD-3**

- Indications for biopsy include both a cut-point as well as the use of multiple variables
- Removed distinction between various PSA levels above the cut point for biopsy (i.e. < 10, > 10)
- PSAV has been incorporated into a set of risk factors to better inform decisions on biopsy
- PCA3 and PHI have been described as markers of specificity, in addition to percent free PSA (i.e. use in those considered for additional biopsy)

**PROSD-4**

- High-grade prostatic intraepithelial neoplasia PIN has been split into multifocal and focal in consideration of repeat biopsy

**Discussion**

- The “Talking Points” section has been removed from the algorithm and incorporated into the discussion
- The discussion has been updated to reflect changes in the algorithm

**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 not all men diagnosed with prostate cancer require treatment. The panel believes that maximizing the detection of early prostate cancer we will increase the detection of both non-aggressive (slow-growing) and aggressive (faster-growing) prostate cancers. The challenge is to accurately identify the biology of the cancer that is detected and thus identify cancers that, if treated effectively, will result in a significant decrease in morbidity and mortality. This variability in prostate cancer behavior causes major concern with the problem of over-treatment resulting in potentially significant adverse implications for quality-of-life issues. The NCCN Prostate Cancer Early Detection Guidelines do not address the treatment of prostate cancer. See the NCCN Treatment Guidelines for Prostate Cancer for prostate cancer treatment recommendations. It is the intention of the panel that these guidelines be linked and, specifically, early detection strategies that do not recognize the importance of refined and selective treatment may result in harm.

The guidelines are specifically for men opting to participate in an early detection program (after receiving the appropriate counseling on the pros and cons). It is the majority opinion of the Prostate Cancer Early Detection Panel Members that there is a growing population of men currently being diagnosed with prostate cancer who can, and should, be monitored for their disease as presented in the NCCN Treatment 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.

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.

See Baseline Evaluation (PROSD-2)
BASELINE EVALUATION

- History and physical (H&P) including:
  - Family history
  - Medications
  - History of prostate disease and screening, including prior PSA and/or isoforms, exams, and biopsies

RISK ASSESSMENT

- Start risk and benefit discussion about offering baseline PSA
- Baseline digital rectal examination (DRE)

EARLY DETECTION EVALUATION

- DRE normal, PSA >1 ng/mL
  - Age 45-49 y (category 2B)
  - Age 70 y (category 2B)

- DRE normal, PSA ≤1 ng/mL
  - Repeat testing at 1-2 year intervals

- DRE normal, PSA <3 ng/mL and no other indications for biopsy
  - Repeat testing at 1-2 year intervals

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.
**INDICATIONS FOR BIOPSY**

- **DRE suspicious for cancer at any PSA level (category 2B)**
  - TRUS-guided biopsy
  - See Management of Biopsy Results (PROSD-4)

- **PSA >3.0 ng/mL<sup>d</sup>**
  - If TRUS-guided biopsy not performed follow up in 6-12 mo with PSA/DRE. Consider use of percent free PSA, PHI, and/or PCA3 in those with serum PSA between 3 ng/mL and 10 ng/mL<sup>f</sup>

- **Excess risk based on multiple factors<sup>e</sup>** (category 2B)
  - Percent free PSA, PHI, or PCA3 in selected patients with serum PSA values between 3 ng/mL and 10 ng/mL<sup>f</sup>

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**TRUS-GUIDED BIOPSY**

**Initial and Repeat**
- Extended-pattern biopsy (12 cores)
  - Number of cores:
    - Sextant (6),
    - Lateral peripheral zone (6), and
    - Lesion-directed at palpable nodule or suspicious image
  - Anteriorly directed biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
  - After 2 negative extended TRUS biopsies, prostate cancer is not commonly found at repeat biopsy. Additional imaging (MRI, T2 weighting, and diffusion weighting) may help identify regions of cancer missed on prior biopsies and should be considered in selected cases.
  - For high-risk men with negative biopsies, consideration can be given to a saturation biopsy strategy (including transperineal techniques) and/or the use of multiparametric MRI followed by an appropriate biopsy technique based on the results.
  - Local anesthesia can decrease pain/discomfort associated with prostate biopsy and should be offered to all patients.

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

<sup>e</sup> Many factors may influence and better inform decisions on biopsy including PSA kinetics and/or velocity. Alternatively, risk calculators could be used in those men similar to cohorts where risk calculators have been developed. These tools combine factors including age, family history, ethnicity, DRE, and PSA to aid in the decision of whom to biopsy. They have not been tested in randomized clinical trials and which cut-point of risk would be associated with a reduction in prostate cancer mortality remains unknown.

<sup>f</sup> Biomarkers that improve the specificity of detection are not recommended as first-line screening tests, but are reserved, for the most part, in selecting those who have undergone at least one negative biopsy for a repeat biopsy. However, there may be some patients who meet either PSA or DRE standards for biopsy, but for whom the patients and/or the physician wish to further define the probability of cancer before undergoing biopsy. A PHI >35, percent free PSA <10% and/or PCA3 score >35 are strongly suspicious for prostate cancer.

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MANAGEMENT OF BIOPSY RESULTS

Cancer → See NCCN Guidelines for Prostate Cancer

Atypia, suspicious for cancer

- Extended pattern rebiopsy (within 6 mo) with increased sampling of the affected site and adjacent areas. If no cancer is found, close follow-up with PSA and DRE is recommended at 1 year interval initially.

- Multifocal (> 2 sites)

- High-grade prostatic intraepithelial neoplasia (PIN)

  - Focal

    → Follow with PSA and DRE at 1 year interval initially (See PROSD-2)

- Benign

  → Repeat biopsy based on risk

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9 It is well known that a negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. Those patients with negative biopsies should be followed with DRE and PSA. Consideration of tests which improve specificity, such as PHI, percent free PSA or PCA3, should be considered in patients thought to be at a higher risk despite a negative biopsy (See PROSD-3). Emerging evidence suggests that the use of multiparametric MRI and/or the use of refined biopsy techniques (transperineal or saturation biopsies) may be of value as well. Also, as noted in the discussion section, PSA testing can be discontinued at certain ages and PSA cutpoints.

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.
Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Introduction

The NCCN Guidelines for Prostate Cancer Early Detection provide a set of sequential recommendations detailing a screening and subsequent work-up strategy for maximizing the detection of prostate cancer that is potentially curable and, if left undetected, represents a risk to the patient. These Guidelines focus on minimizing unnecessary procedures and limiting, to some extent, the detection of indolent disease. These Guidelines were developed for men who have elected to participate in the early detection of prostate cancer. The Panel does not support unselected and uninformed population-based screening. The panel supports screening only in healthy men, at any age. Any clinician who uses these guidelines is expected to exercise independent medical judgment in the context of individual clinical circumstances, and to incorporate patient preferences in deciding how to apply these guidelines.

Overview

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths in American men. In 2014, it is estimated that 233,000 men will be diagnosed with prostate cancer and 29,480 will die of this disease.1

Over the last 2 decades in the United States, death rates for prostate cancer have fallen 45%, largely due to early detection and/or improved treatment.6

The Panel supports the continued use of PSA testing for the early detection of prostate cancer in informed, healthy men in certain age groups. The Panel bases this recommendation on randomized trials that observed a reduction in prostate cancer-specific mortality in men who underwent PSA screening.

However, the Panel also uniformly acknowledges the risk of overdetection of otherwise indolent disease and the attendant risk of overtreatment, which exposes men to the potential morbidity of treatment without benefit. The Panel concludes that Early Detection Guidelines should be linked to the NCCN Guidelines for Prostate Cancer, which explicitly recommends active surveillance for appropriate candidates.

Types of Early Detection Testing

DRE

Currently, best evidence supports the use of serum PSA for the early detection of prostate cancer. Currently, 81% of prostate cancers are pathologically organ-confined at time of diagnosis.7 Studies have consistently shown that prostate cancer cases detected through PSA testing are more often confined to the prostate than those detected solely by digital rectal examination (DRE).8,9

Still, many experts continue to recommend DRE for screening, as some clinically significant cancers may potentially be missed using a serum PSA cut point alone. Yet while previous studies suggested that DRE is a robust screening test for prostate cancer, its role in contemporary practice is uncertain. For example, among 5519 men in the control arm
of the Prostate Cancer Prevention Trial (PCPT) with a normal DRE and PSA <3.0 ng/mL, Thompson and colleagues\(^10\) observed that an abnormal DRE increased the probability of cancer detection by almost 2.5 fold. However, these investigators also reported that family history and DRE added very little to cancer detection compared to using PSA alone, with an absolute difference of only 0.02 in the area under the curve (AUC) for detecting any prostate cancer.

Recent screening trials have either used DRE in conjunction with PSA for screening,\(^11\) or as an ancillary test for patients who are found to have an elevated PSA.\(^12,13\) To elucidate the specific role of DRE in screening for prostate cancer, Gosselaar and colleagues\(^14\) showed that in those with a serum PSA >3 ng/mL, those with a positive DRE were more likely to have prostate cancer. Others have shown a survival benefit of DRE in identifying cancers associated with normal serum PSA levels (<2.5 ng/mL), lending support to a potentially beneficial role of DRE in identifying more aggressive tumors.\(^15\)

Therefore, the Panel recommends DRE as a complementary test with serum PSA in asymptomatic men and believes DRE should be performed in all men with an abnormal serum PSA.

**PSA Testing**

When the first recommendations for early detection programs for prostate cancer were made, serum total 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.

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, consideration should be given to repeat testing, particularly if the value is close to the threshold.

**Factors Affecting PSA Levels**

PSA can be elevated due to infection, recent instrumentation, ejaculation, or trauma. There appears to be little value to empiric antibiotic use for improving test performance in asymptomatic men with an elevated PSA.\(^16\)

The 5α-reductase inhibitors (5-ARI) finasteride and dutasteride are commonly used to treat lower urinary tract symptoms due to benign prostatic hyperplasia (BPH). Use and duration of 5-ARI therapy should be elicited carefully in the history, as this class of drugs typically results in an approximate 50% decrease in serum PSA levels within 6 to 12 months of initiating therapy. However, this effect is tremendously variable. For example, one study showed that after 12 months of treatment, only 35% of men demonstrated the expected 40% to 60% decrease in PSA, while another 30% had greater than a 60% decrease.\(^17\) Thus, the commonly employed method of doubling the measured PSA value to obtain an adjusted value may result in unreliable cancer detection. PSA can be affected in men taking 1 mg/day of finasteride (Propecia) as well.\(^18\)

Nonetheless, failure to achieve a significant PSA decrease can indicate a heightened risk for prostate cancer that warrants regular testing.
Results from several clinical trials suggested that 5-ARIs enhance the predictive capacity of PSA,\textsuperscript{19,20} but reflex ranges for PSA among patients on 5-ARI’s have not been established. The PCPT of 18,882 men demonstrated that finasteride reduced the incidence of prostate cancer by 25% compared to placebo. This reduction was almost exclusively for low-grade (Gleason sum 6) tumors; there was an increased proportion of aggressive (Gleason sum $\geq 7$) tumors.\textsuperscript{21} However, after 18 years of follow-up, there was no significant group difference in overall survival or survival after the diagnosis of prostate cancer in those on finasteride compared to the control group.\textsuperscript{22}

In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, PSA detected more high-grade tumors in the dutasteride arm, while the overall prostate cancer diagnosis fell by 23% compared to control.\textsuperscript{20} Similar to the PCPT trial, the difference in the number of high grade cancers detected did not seem to result in a mortality difference.\textsuperscript{23}

A report on the Combination of Avodart (dutasteride) and Tamsulosin (CombAT) trial also showed a 40% lower incidence of prostate cancer with dutasteride plus tamsulosin (another BPH drug) compared to tamsulosin alone, along with a slightly improved yield of PSA-driven biopsy.\textsuperscript{24} Unlike the PCPT and REDUCE studies, diagnosis of aggressive (high grade) tumors was not increased. Overall, these studies suggest that PSA testing may have enhanced specificity for men receiving finasteride or dutasteride. Whether or not men should consider taking these agents for chemoprevention is beyond the scope of this guideline.

Ketoconazole, commonly used to treat fungal conditions, inhibits the androgen synthesis pathway and hence can also lower PSA levels. Since moderate PSA decreases have been observed with ketoconazole in the treatment of patients with prostate cancer after failure of hormonal therapy,\textsuperscript{25} recent ketoconazole use should also be noted in the history.

A health survey on 12,457 men visiting a prostate cancer screening clinic showed that over 20% of men take herbal supplements, while only 10% take prescription medication (such as finasteride) for lower urinary tract symptoms.\textsuperscript{26} 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.

Overall, appropriate use of PSA alone can provide a diagnostic lead time of nearly 5 to 10 years but the lead time is variable across studies, populations and screening protocols.\textsuperscript{27} PSA examination results in detection of earlier organ-confined disease.\textsuperscript{28} The risk of prostate cancer increases with increasing PSA but there is no level of PSA below which the risk of prostate cancer can be eliminated. The PCPT demonstrated that 15% of men with a PSA level of 4.0 ng/mL or less and a normal DRE had prostate cancer (as diagnosed by end-of-study biopsies).\textsuperscript{29} Approximately 30% to 35% of men with serum PSAs in the 4 to 10 ng/mL range will be found to have cancer. Total PSA levels $>10$ ng/mL confer a greater than 67% likelihood of harboring prostate cancer.\textsuperscript{30}

**Controversies of PSA Testing**

The decision about whether to pursue early detection of prostate cancer is complex. When, who and how often to test remain major topics of debate. PSA screening has played a critical role in the downward migration of prostate cancer stage seen over the past decade. The rate of metastatic disease at the time of diagnosis has...
decreased dramatically since 1988. There has been considerable stage migration in the past 2 decades in the United States as a result of early detection strategies and this trend has likely, but not positively, contributed, in part, to a significant reduction in prostate cancer mortality.

Still, although prostate cancer is a major cause of death and disability in the United States, many argue that the benefits of early detection are, at best, moderate and that early detection results in the identification of many men with indolent disease (overdetection) which is too often compounded by unnecessary treatment without benefit (overtreatment). In addition, PSA testing often produces false positive results, which in turn contribute to patient anxiety with 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 United States Preventive Services Task Force (USPSTF) has recommended against routine PSA testing.

**Population-Based Screening Studies**

Although many trials have been cited with regard to PSA testing, 2 studies are most relevant due to their topicality and randomized design.

**ERSPC Trial**

The ERSPC involved about 182,000 men between the ages of 50 and 74 years in 7 European countries, randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. The predefined core group included 162,388 men aged 55 to 69 years. Death from prostate cancer was the primary outcome. During a median follow-up of 11 years, the cumulative incidence of prostate cancer was 7.4% in the screening group versus 5.1% in the control group. There were 299 prostate cancer deaths in the screening group compared to 462 in the control. The rate ratio for death from prostate cancer was 0.79 for the screening arm as compared to control (95% CI, 0.68–0.91; \( P = .001 \)). The investigators concluded that the PSA-based screening program reduced mortality from prostate cancer by 21%. At the time of publication, the authors stated that 1055 men would need to be screened and 37 additional men would need to be treated over 11 years to prevent one death from this malignancy. Over the long term, the number need to screen and the additional number needed to treat are much lower (200 and 5 respectively). Modeling the ERSPC data, Heijnsdijk and colleagues estimated the number needed to screen was 98 and number needed to treat was 5 to save one life.

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

The Göteborg randomized population-based prostate cancer screening trial was initiated before and independently of the ERSPC, but some of its patients were reported as part of the ERSPC. Twenty thousand men aged 50 to 64 years were randomized to either a screening group invited for PSA testing every 2 years or to a control group not invited. The study is ongoing, with men who have not reached the upper age limit invited for PSA testing. In men randomized to screening, 76% attended at least one test. PSA testing in the general population was very low at the beginning (3%) but it increased over time.

During a median follow-up of 14 years, 1138 men in the screening group and 718 in the control group were diagnosed with prostate cancer, resulting in a cumulative prostate cancer incidence of 12.7% in the screening group and 8.2% in the control group (HR, 1.64; 95% CI,
The rate ratio for death from prostate cancer was 0.56 (95% CI, 0.39–0.82; \( P = .002 \)) in the screening compared with the control group. Overall, 293 men needed to be screened and 12 needed to be diagnosed to prevent one prostate cancer death over 14 years. This study shows that prostate cancer screening is acceptable to the Swedish population and that prostate cancer mortality was reduced almost by half over 14 years. In addition, it should be noted that a cause-specific survival benefit was noted despite the fact that not all cancers were immediately treated. This suggests that early detection combined with selective treatment based on risk can lower mortality rates without uniform treatment of all cancers.

There are several possible explanations for the more favorable results of the Göteborg trial compared to the PLCO or ERSPC trials. First, the patients were younger and less likely to have incurable prostate cancer at first screening; second, there was less contamination of the control arm because PSA testing was uncommon in the Swedish population when the study began; third, a lower PSA threshold was used for recommending a biopsy; and finally, men were screened more frequently than ERSPC and for a longer period than PLCO. However, the Göteborg trial results should not be interpreted as independent confirmatory study, as more than half of the patients were included in the main analysis of ERSPC. A recent analysis of the Göteborg trial showed that, 9 years after the cessation of screening, the risks of high-risk disease and mortality became similar in the screening and control arms.\(^1\)

In a similar fashion, the Finnish Prostate Cancer Screening Trial, the largest component of ERSPC, reported their results. At 12 years, a small, non-statistically significant reduction in prostate cancer specific death was noted.\(^2\)

**PLCO Trial**

The PLCO study randomized 76,685 men aged 55 to 74 years at 10 U.S. study centers to annual screening (annual PSA for 6 years and DRE for 4 years) or usual care.\(^3\) After 13 years of follow-up, the incidence rate ratio for the screening arm compared to control 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 group and of the control (RR, 1.09; 95% CI, 0.87–1.36). Despite the impressive sample size, this trial is flawed by prescreening and the high contamination rate of 40% to 52% each year in the control group (i.e. 74% of men in the usual care arm were screened at least once). The estimated mean number of screening PSAs (DREs) in the control arm was 2.7 (1.1); this compared to 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 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.\(^4\)

In a subset analysis reported by Crawford and colleagues,\(^5\) a 44% decrease in the risk of prostate cancer-specific death was observed in men with no or minimal comorbidity assigned to screening compared to control, and the numbers needed to screen and treat to prevent one death were 723 and 5, respectively. This benefit was not found among men with one or more significant comorbidities. These results suggest that screening is more useful among men in good health due to the lack of competing cause for mortality. However, others suggest there are major methodological errors in such an analysis.\(^6\)
**Trial Limitations**

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

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

**Practical Considerations of Testing**

**Age At Which to Initiate Testing**

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

As younger men were not included in these screening studies, baseline testing at earlier ages has not been evaluated in RCTs. However, observational evidence suggests that baseline testing of men in their 40s and early 50s may have value for future risk stratification, although some would describe it as marginal. A study by Lilja and colleagues assessed blood collected from 21,277 men in Sweden aged 33 to 50 years who were followed until 2006. Among the 1312 cases of prostate cancer and 3728 controls without prostate cancer, these investigators reported that a single PSA test before age 50 years predicted subsequent prostate cancer up to 30 years later with a robust AUC of 0.72 (0.75 for advanced prostate cancer). This suggests that one could perform early, baseline testing and then determine the frequency of testing based on risk.

A recent report clarified associations of age with the long–term risks of metastases. In this study, the risk of prostate cancer death was strongly correlated with baseline PSA in men aged 45 to 49 years and 51 to 55 years; 44% of the deaths in the analytic cohort occurred in men in the highest tenth of the distribution of PSA, suggesting that there may be a strong rationale for baseline testing in men younger than age 55 years. Although many advocate earlier testing only in men thought to be at higher risk due to family history or ethnicity, as noted previously, 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 favored baseline, informed testing beginning at ages 45 to 50 years, annual to biannual testing in those above the age-specific median PSA and retesting at age 50 in those below the median. The median PSA levels are 0.7 ng/mL and 0.9 ng/mL for ages 40 to 49 and ages 50 to 59, respectively. Annual or biannual follow-up is recommended for men who have a PSA value ≥1.0 ng/mL. This is above the 75th percentile for younger men (<50 years).
**Frequency of Testing**

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

A recent comparison of two centers involved in the ERSPC trial studied the impact of different screening intervals on the diagnosis of interval cancers in men aged 55 to 64 years. The Göteborg arm randomized 4202 men to screening every 2 years, while the Rotterdam arm randomized 13,301 men to screening every 4 years with similar follow up of 11 to 12 years. Compared to screening every 4 years, there was a significant, 43% reduction in the diagnosis of advanced prostate cancer (clinical stage >T3a, N1, or M1; PSA >20 ng/mL; Gleason >8 at biopsy) for screening every 2 years. However, there was also a 46% increase in the diagnosis of low-risk prostate cancer (clinical stage T1c, Gleason <6, and PSA <10 ng/mL at biopsy) for screening every 2 years.

Another study using micro-simulation models of prostate cancer incidence and mortality predicted that a strategy that utilizes biennial intervals in men with average PSA levels and longer screening intervals (every 5 years) for men with low PSA levels (below median for age by decade) allows a 2.27% risk of prostate cancer death compared to 2.86% from no screening. In addition, compared to annual screening and using a biopsy threshold of 4.0 ng/mL, the biennial strategy also projected a relatively lower over-diagnosis rate of 2.4% (vs. 3.3% for annual screening), 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.

These data thus suggest that screening every two years may provide comparable survival to annual screening while allowing modest reductions in overdiagnosis and significant reductions in unnecessary testing. However, Panel members did not uniformly agree on the recommendation for biannual screening; some favored annual screening.

**Age At Which to Discontinue Testing**

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

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

Since the previously cited RCTs (ESRPC, PLCO, and Göteborg) observed benefits to testing only in men aged up to 70 years, several panelists favored stopping testing at age 70 years.

However, other data would suggest a benefit to screening beyond 70 years. A study of 4561 men who underwent radical prostatectomy found that men older than 70 years were more likely to have higher grade and stage of disease and worse survival compared to their younger counterparts. Others have published similar findings.

To assess the appropriate ages for discontinuing screening, the previously cited micro-simulation model predicted that decreasing the stopping age from 74 to 69 years would lead to a 27% relative...
reduction in the probability of life saved, but an almost 50% reduction in the probability of overdiagnosis. This latter finding reflects the fact that a large proportion of men older than 70 years have cancer that would be unlikely to diminish their life expectancy, and that screening in this population would substantially increase rates of over detection, while also recognizing the increased prevalence of higher-risk cases in this age that could benefit from earlier detection.

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

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

In summary, one strategy to reduce over-diagnosis in the older population would be to discontinue screening at age 69 years; a second would be to continue screening up to age 74 years but increase the PSA threshold for biopsy among men aged 70 to 74 years; and a third would be to discontinue screening at age 75 years for men with PSA <3.0 ng/mL.

Indications for Biopsy

The previously cited RCTs used PSA thresholds to prompt a biopsy. PSA cut-points for biopsy varied somewhat between centers and trials over time. Although a serum PSA of 2.5 ng/mL has been used by many, a level of 3 ng/mL is supported by the trials and would more robustly limit the risk of overdetection. However, some panel members did not recommend limiting the option of biopsy to pre-specified PSA thresholds, noting that there are many other factors (eg, age, ethnicity, family history, PSA kinetics) that should also inform the decision to perform biopsy. Several panel members also noted that risk calculators could be used in appropriately selected men.

Prostate cancer risk calculators have been developed to estimate an individual’s risk for prostate cancer from multiple factors. Common calculators are the Sunnybrook, ERSPC and PCPT-based risk calculators. These online tools combine clinical variables—including but not limited to age, family history, ethnicity, DRE, and PSA—to estimate both the risk of biopsy-detectable prostate cancer and the risk of biopsy-detectable high-grade prostate cancer. Such information potentially allows for more informed decision-making. However, such calculators have not been assessed in randomized clinical trials and which cut point of risk, which would be associated with a reduction in prostate cancer mortality, is unknown. Such calculators have as much value in determining who might not need biopsy as in identifying those at higher risk.
Biopsy Technique

Initial Biopsy

Systematic prostate biopsy under transrectal ultrasound (TRUS) guidance is the recommended technique for prostate biopsy. Initially described as a sextant technique sampling both right and left sides from the apex, mid-gland and base in the mid-parasagittal plane, more recently extended biopsy schemes have demonstrated improved cancer detection rates. Although no one scheme is considered optimal for all prostate shapes and sizes, most emphasize better sampling of the lateral and anterior aspects of the peripheral zone. One commonly used scheme is the 12-core biopsy scheme that includes a standard sextant as well as a lateral sextant scheme (lateral apex, lateral mid-gland, lateral base). This scheme has been validated and results in enhanced cancer detection compared to sextant biopsy schemes.\(^{67,68}\)

The Panel recommends an extended-pattern, at least 12-core biopsy with sextant (6) and lateral peripheral zone (6) and lesion-directed palpable nodule or suspicious image. 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.

Up to 90% of men undergoing a prostate biopsy have reported some discomfort during the procedure.\(^ {69}\) Both topical lidocaine gel and an injectable nerve block have been shown to be safe and efficacious for reducing discomfort.\(^ {70,71}\) Topical lidocaine was more efficacious in reducing pain during probe insertion, whereas peri-prostatic injection reduced pain during the biopsy itself. These minor anesthetic techniques greatly enhance the acceptability of the procedure, particularly with extended templates and saturation techniques, but should be considered in all patients.\(^ {72}\) For exceptional cases such as men with anal strictures or patients who have been inadequately blocked with a periprostatic injection, intravenous sedation or general anesthesia may be advantageous.

Interest in the use of novel imaging, particularly MRI, to guide needle placement during biopsy (see Novel Imaging) has increased recently. Until these methods are validated in ongoing clinical trials, however, the Panel at present does not recommend specific imaging techniques other than baseline TRUS.

In addition, there is interest in transperineal approaches to biopsy (often image-guided) to improve diagnostic accuracy and decrease the risk of infection.\(^ {73,74}\) However, at present the Panel does not recommend routine use of transperineal biopsy.

Risks of Biopsy

The problem of over-biopsy is gaining attention in the PSA debate, due to increasing concerns about the risks of complications, particularly drug-resistant *Escherichia coli* infections.\(^ {75}\) The range of potential infectious complications includes urinary tract infection (UTI), epididymitis, orchitis, prostatitis, and sepsis. Other morbidities include rectal bleeding, hematuria, vasovagal episodes, fever, hematospermia, and dysuria.\(^ {76}\)

In an analysis of 17,472 men in the SEER database, prostate biopsy was associated with a 2.7-fold increased risk of 30-day hospitalization.\(^ {77}\) These investigators also reported that while the incidence of infectious complications following prostate biopsy has increased significantly in recent years, the incidence of noninfectious complications has remained relatively stable. These results are similar to those from a Canadian study of 75,190 men who were biopsied, in which the hospitalization rate increased from 1.0% in 1996 to 4.1% in
About 70% of all admissions were related to infections. A recent analysis of the PLCO trial, however, observed that biopsy complications were infrequent and that biopsy was not associated with a higher risk of mortality.79

Fluoroquinolones, particularly ciprofloxacin, are used commonly as a prophylaxis for TRUS biopsy. Recent studies have reported that about half of post-biopsy infections are resistant to fluoroquinolone, many of which are also resistant to other antibiotics.80,81 Resistance is associated with prior prophylactic exposure to fluoroquinolone.82,83 Although these infections will respond to cephalosporins, measures are needed to prevent additional resistant strains. One strategy is to develop more stringent criteria for biopsy. Another proposed strategy is to selectively target antibiotic prophylaxis with pre-biopsy rectal culture.84

PSA Derivatives and other Tests

Age- and Race-Specific PSA Reference Ranges

Age-specific PSA reference ranges were introduced by Oesterling and colleagues85 as a method to increase cancer detection (ie, increase sensitivity) in younger men by lowering PSA cutoffs for biopsy and to decrease unnecessary biopsies (ie, improve specificity) in older men by increasing PSA cutoffs.85-87 Several groups have investigated these age-specific ranges with equivocal results. Others have suggested race-specific reference ranges.88 However, the exact roles of these age- and race-specific PSA cutoffs in the early detection of prostate cancer remain unclear. The Panel has no recommendations regarding routine use of these ranges.

PSAV

The rate of change in PSA over time is broadly termed PSA velocity (PSAV), determined by at least 3 separate PSA values calculated over at least an 18-month period. Carter and colleagues89 first showed that PSAV is greater in men eventually diagnosed with prostate cancer than in men not diagnosed with the disease and suggested its use as a screening tool. In a subsequent study of 980 men enrolled in the BLSA, Carter and colleagues explicitly linked PSAV with the risk of prostate cancer death by observing that PSAV recorded 10 to 15 years before cancer diagnosis (commonly with PSA < 4 ng/mL) was associated with disease-specific survival up to 25 years later: the relative risk of prostate cancer death was higher in men with PSAV >0.35 ng/mL/y compared to those with PSAV ≤0.35 ng/mL/y or less (RR, 4.7; 95% CI, 1.3–16.5; P = .02).90 These data provide support that PSAV may help identify lethal cases. However, the small number of deaths from prostate cancer (20) precludes definitive conclusions.

In two other studies of men with prostate cancer,91,92 very high PSAV (>2 ng/mL/y) during the year before diagnosis was associated with a greatly increased risk of death from the disease, but this is a much higher cutoff for PSAV than the one proposed by Carter and colleagues.

Vickers and colleagues,93 however, have questioned the role of PSAV in tumor detection among men with low PSA levels. The analysis was performed on 5519 men undergoing biopsy regardless of indication in the control arm of the PCPT to explore the additional yield from a PSA threshold of 0.35 ng/mL/y. The main finding of this study was that PSAV did not significantly increase the predictive accuracy of high PSA levels or positive DRE and might substantially increase the number of men recommended for biopsy. However, these findings should be
applied only to men similar to those studied in PCPT (≥55 years of age; 96% Caucasian-American; 17% family history of prostate cancer, PSA values ≤3 at enrollment). A recent report suggests that screening strategies that utilized PSAV at low PSA levels were more likely to suffer from overdiagnosis and false-positive tests resulting in more harm relative to incremental lives saved.

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

In a recently reported study of men pursuing a second biopsy after an initial negative biopsy, PSAV was an independent predictor of overall prostate cancer, intermediate and high-grade cancer.

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

%f PSA

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

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

The U.S. Food and Drug Administration (FDA) approved the use of %fPSA for the early detection of prostate cancer in men with PSA levels between 4 ng/mL and 10 ng/mL. 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.

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

cPSA

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

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

PSAD

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

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

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

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

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

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

PCA3

PCA3 is a noncoding, prostate tissue-specific RNA that is overexpressed in prostate cancer. Current assays quantify PCA3 over
expression in post-DRE urine specimens. PCA3 appears useful in predicting biopsy outcomes at both initial and repeat biopsies. However, it appears most useful in determining which patients should undergo a repeat biopsy.\textsuperscript{113-116}

The FDA has approved the PCA3 assay to help decide, along with other factors, whether a repeat biopsy in men age 50 years or older with one or more previous negative prostate biopsies is necessary.

**Newer Biomarkers or Combinations of Biomarkers**

Development of novel biomarkers continues. The prostate health index (PHI) is a combination of existing tests (tPSA, fPSA, proPSA).\textsuperscript{117-119} It was assessed in a multi-center study and was noted to have approximately doubled the sensitivity of F/T PSA for cancer detection in those with serum PSA concentrations between 2 and 10 ng/dL.\textsuperscript{120} In addition, the PHI correlated with cancer grade. The PHI was approved by the FDA for use in 2012 in those with serum PSA values between 4 and 10 ng/mL. The 4-kallikrein panel (another combination of tests) appears to have value as well.\textsuperscript{121} However, the panel does not recommend these tests as first line screening tests in all patients as yet given limited prospective analyses in U.S. populations.

**Novel Imaging**

There is considerable interest in the use of novel imaging, most notably multiparametric MRI to either select those who need a prostate biopsy or to guide needle placement during the biopsy.\textsuperscript{122-125} Clinical trials are underway to assess the value of MRI imaging in this regard. Until such trials are completed, the Panel does not recommend baseline imaging before a diagnosis of prostate cancer is made.
educate patients about the distinction between these two diseases when discussing the risks and benefits associated with early detection.

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

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

- The panel uniformly feels that these guidelines need to be linked to NCCN Guidelines for Prostate Cancer.

- The Panel recommends that baseline PSA testing should be offered to healthy, well-informed men aged 50 to 70 years based on the results of randomized clinical trials. The majority of panelists believed that baseline testing should be offered to men aged 45 to 49 years. Baseline testing may be complemented by DRE.

- The Panel recommends frequency of testing be one to two years. For men aged 45 to 49 years with serum PSA values below 1 ng/mL, additional testing may be deferred until age 50 years. For men with PSA exceeding 1.0 ng/mL, testing should occur at 1- to 2-year intervals.

- The Panel recommends that biopsy should be considered in those aged 50 to 70 years with a positive DRE and/or a serum PSA > 3.0 ng/mL. However, the majority of panel members agreed 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, ethnicity, health status, and patient preference.

- The Panel recommends that PSA testing be individualized after the age of 70 years and that indication for biopsy be carefully evaluated. Panel members uniformly discouraged PSA testing in men unlikely to benefit from prostate cancer diagnosis based on age and/or comorbidity.

- The Panel recommends that consideration may be given to biomarkers that improve specificity such as %fPSA, PHI, and PCA3, although these biomarkers are indicated more strongly in the consideration of repeat biopsy after an initially benign result.

### Interpretation of Biopsy Results

#### Cancer

Patients diagnosed with prostate cancer by biopsy should be managed according to the NCCN Guidelines for Prostate Cancer. Among men diagnosed with cancer on prostate biopsy, the Panel does not recommend repeat biopsy, except in special circumstances, such as the suspicion that the patients harbors more aggressive cancer than was evident on the initial biopsy and the patient is otherwise a candidate for active surveillance as outlined in the Treatment Guidelines.
High-Grade Prostatic Intraepithelial Neoplasia

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

Interestingly, the rates of cancer with repeat biopsy in such patients seems to be little different than those who undergo repeat biopsy based on other risk factors, such as age, family history, PSA, etc. In addition, most cancers detected are low grade. If extended biopsies were used initially, only those at high risk for more aggressive cancer should undergo repeat biopsy. It is recommended that those with multifocal HGPIN be considered for repeat biopsy at 6 months.

Atypia, Suspicious For cancer

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

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

Therefore, the Panel recommends a repeat extended biopsy scheme within 3 to 6 months of an initial atypia diagnosis with additional cores obtained from the region demonstrating atypia. If no cancer is found on the repeat biopsy, close follow-up with DRE and PSA is recommended.

Benign Results

If a biopsy returns as negative for cancer, the Panel recommends follow-up based on PSA and DRE findings. Consideration for repeat biopsy may be based on risk stratification and/or the use of biomarkers that improve specificity, such as PCA3 and %PSA. As mentioned, multiparametric MRI may play an increasingly important role in the evaluation of such patients. Such imaging may be complemented by targeted biopsy.

Summary

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

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

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