



NCCN Clinical Practice Guidelines in Oncology™

# Prostate Cancer Early Detection

V.2.2010

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This discussion is being updated to correspond with the newly updated algorithm.

**Clinical Trials:** The 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](#)

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2009.

Summary of changes in the 2.2010 version of the Prostate Cancer Early Detection Guidelines include:

- The addition of the updated [Discussion section](#).

Summary of changes in the 1.2010 version of the Prostate Cancer Early Detection Guidelines include:

#### [PROSD-1](#)

- The Guidelines are specifically for men opting to participate in an early detection program (after receiving the appropriate counseling on the pros and cons of early detection).

#### [PROSD-2](#)

- Footnote “a” has been modified. “Screening in men over 75 y should be considered individually.” Previously recommended individualized screening in men over 80 y.
- Under Screening and Follow-Up, the PSA value was changed from 0.6 ng/mL to 1.0 ng/mL with the addition of a footnote. Footnote “e” states “The PSA value of 1.0 ng/mL selects for the upper range of PSA values for 40-49 year-old men.”
- Footnote “g” is new to the page. “Less frequent PSA/DRE follow-up in the older patient may be appropriate based on their individual risk stratification.”

#### [PROSD-A \(page 2 of 3\)](#)

- Level 1 evidence for PSA screening is now available through a European study released in 2009. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in the early 1990's to evaluate the effect of prostate-specific antigen (PSA) testing on death rates from prostate cancer. The trial involved 182,000 men between the ages of 50 and 74 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 162,243 men of ages of 55-69 years. Death from prostate cancer was the primary outcome. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. There were 214 prostate cancer deaths in the screening group, and 326 in the control group. The rate ratio for death from prostate cancer in the screening group, compared to the control group, was 0.80 (95% confidence interval [CI], 0.65-0.98; adjusted P=0.04). The researchers concluded that PSA-based screening reduced the rate of death from prostate cancer by 20%. However, they also concluded that this was associated with a high risk of over-diagnosis. Statistically, 1,410 men would need to be screened and 48 men would need to be treated to prevent one death from prostate cancer

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UPDATES

## INTRODUCTION

It is neither the intent nor the suggestion of the panel that all men diagnosed with prostate cancer require treatment. It is inherent that as we maximize 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 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 tumor behavior is unlike any other cancer and, consequently, causes major concern with the problem of over treatment resulting in potentially significant adverse implications on quality of life issues (eg, urinary, bowel and erectile dysfunction). The natural history of prostate cancer is that it will progress over time, but the unanswerable question is over what period of time.

The Prostate Cancer Early Detection guidelines do not address the treatment of prostate cancer. 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 Prostate Cancer Treatment Guidelines. The guidelines for a baseline PSA and lowering the PSA thresholds for biopsy were recommended by most panel members, but a consensus was not reached.

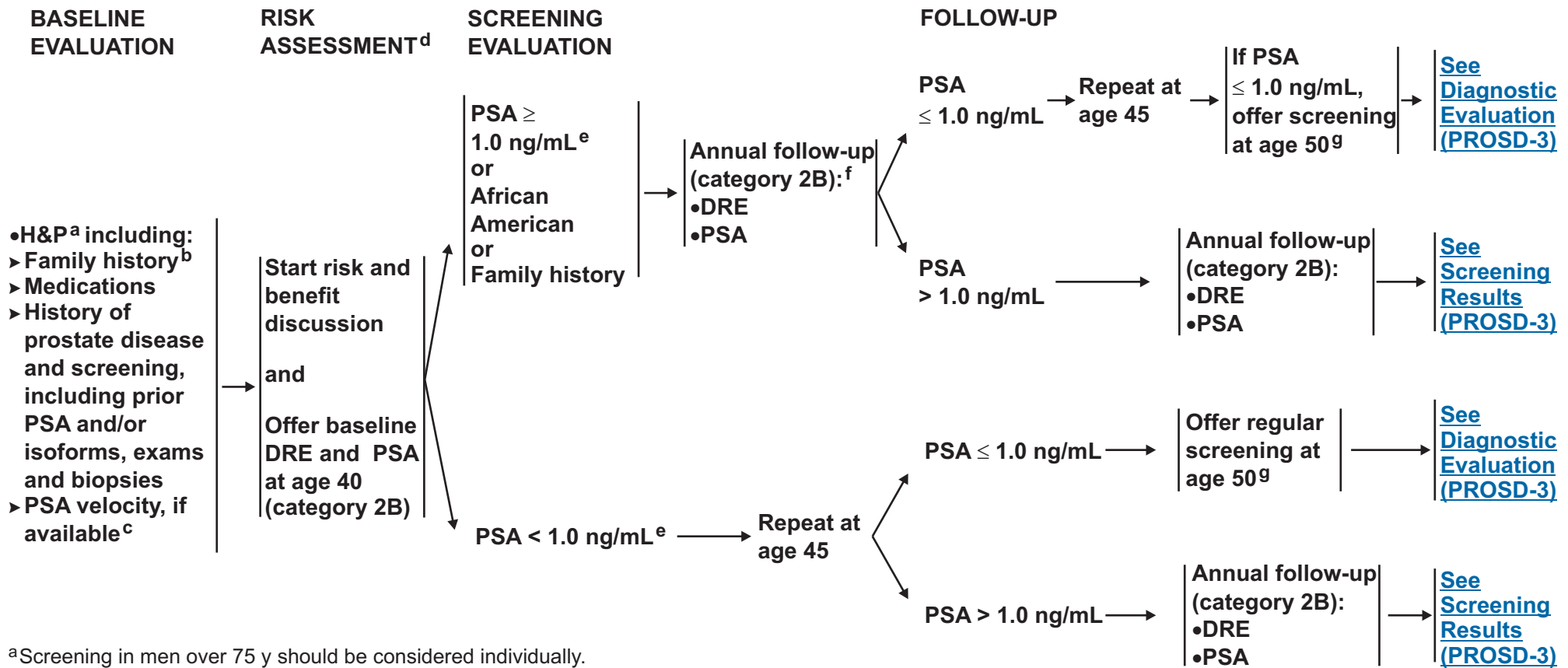
The guidelines are continuously in a state of evolution and the panel will incorporate changes based on new evidence and expert opinion and provide a rating of consensus with respect to each recommendation.

[See Suggested “talking points” to cover in a discussion with a potential screenee about the pros and cons of PSA testing \(PROSD-A\).](#)

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[See Baseline Evaluation \(PROSD-2\)](#)



<sup>a</sup>Screening in men over 75 y should be considered individually.

<sup>b</sup>Family history may affect a decision to biopsy. The closer the relative, the earlier the onset and the more affected family members, the higher the risk.

<sup>c</sup>PSA Velocity: For men with PSA < 4 ng/mL, data suggest that a PSA velocity of ≥ 0.35 ng/mL/y is suspicious for the presence of cancer (Carter HB, Ferrucci L, Kettermann A et al. Detection of Life-Threatening Prostate Cancer With Prostate-Specific Antigen Velocity During a Window of Curability. J Natl Cancer Inst 2006;98(21):1521-1527); for men with PSA 4-10 ng/mL, a PSA velocity of ≥ 0.75 ng/mL/y is suspicious for cancer. PSA velocity in men with PSA > 10 ng/mL has not been determined useful. Measurement should be made on at least three consecutive specimens drawn over at least an 18-24 mo interval. There is variability. Longer time periods increase reliability, but, as calculation of PSA velocity over longer prior time intervals usually decreases the PSA velocity estimate, it might decrease predictive power. It is also important to remember that biologic variability and/or prostatitis may be confounding factors in determining PSA velocity; therefore, antibiotic therapy and repeated PSA measurements may be considered to minimize these sources of confusion.

<sup>d</sup>See Introduction (PROSD-1)

<sup>e</sup>The PSA value of 1.0 ng/ml selects for the upper range of PSA values for 40-49 year-old men.

<sup>f</sup>There is no evidence in the literature to support the follow-up recommendations listed; they represent the consensus-based opinions of the panel based upon their clinical experience.

<sup>g</sup>Less frequent PSA/DRE follow-up in the older patient may be appropriate based on their individual risk stratification.

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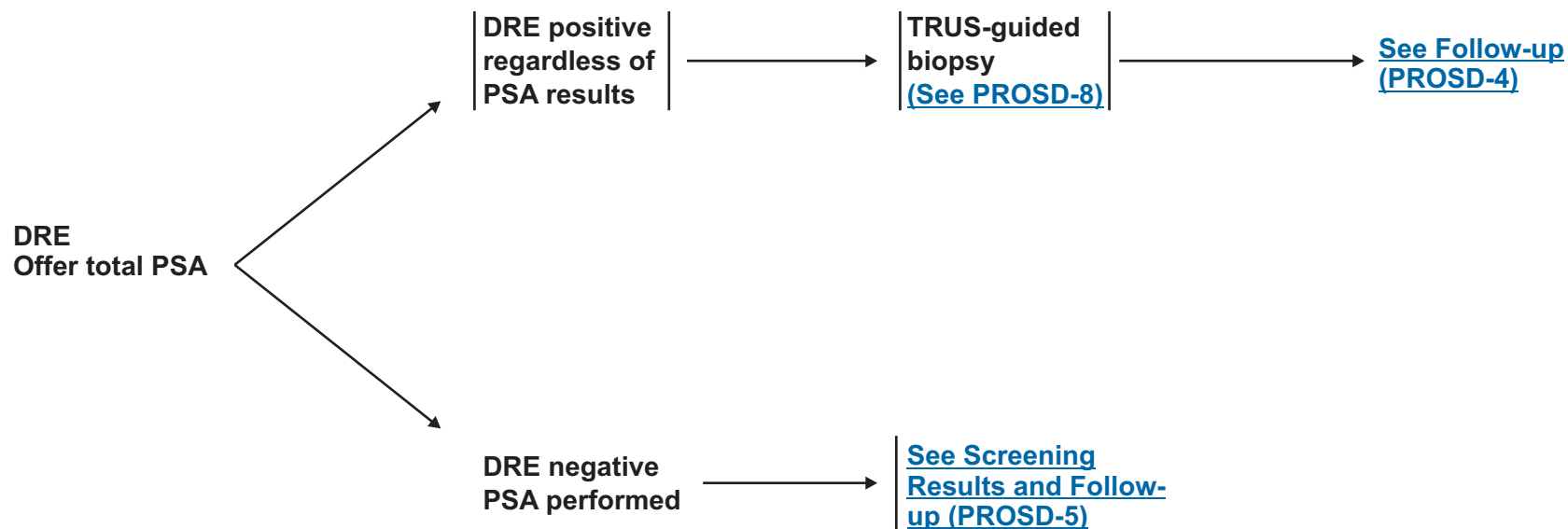
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**DIAGNOSTIC  
EVALUATION**

**SCREENING  
RESULTS**

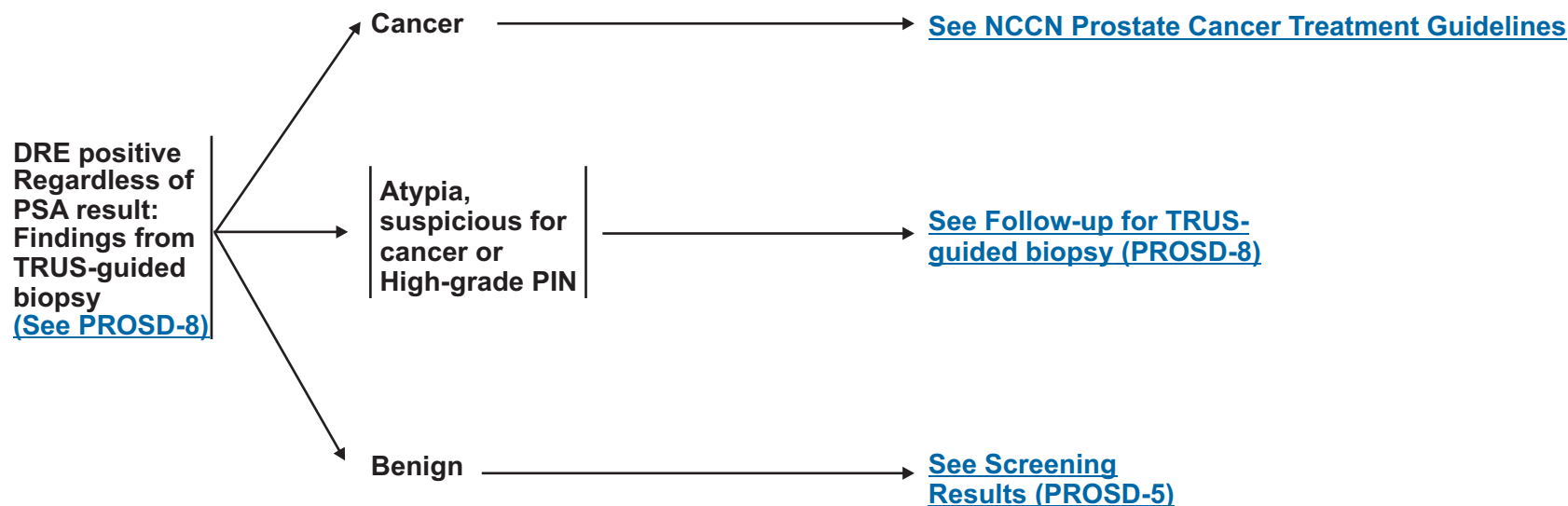
**FOLLOW-UP**



<sup>h</sup>In patients using finasteride or dutasteride, failure to have a substantial decrease (approximately 50%) in PSA or an increase while on medication can be associated with an increased risk of prostate cancer.

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## FOLLOW-UP



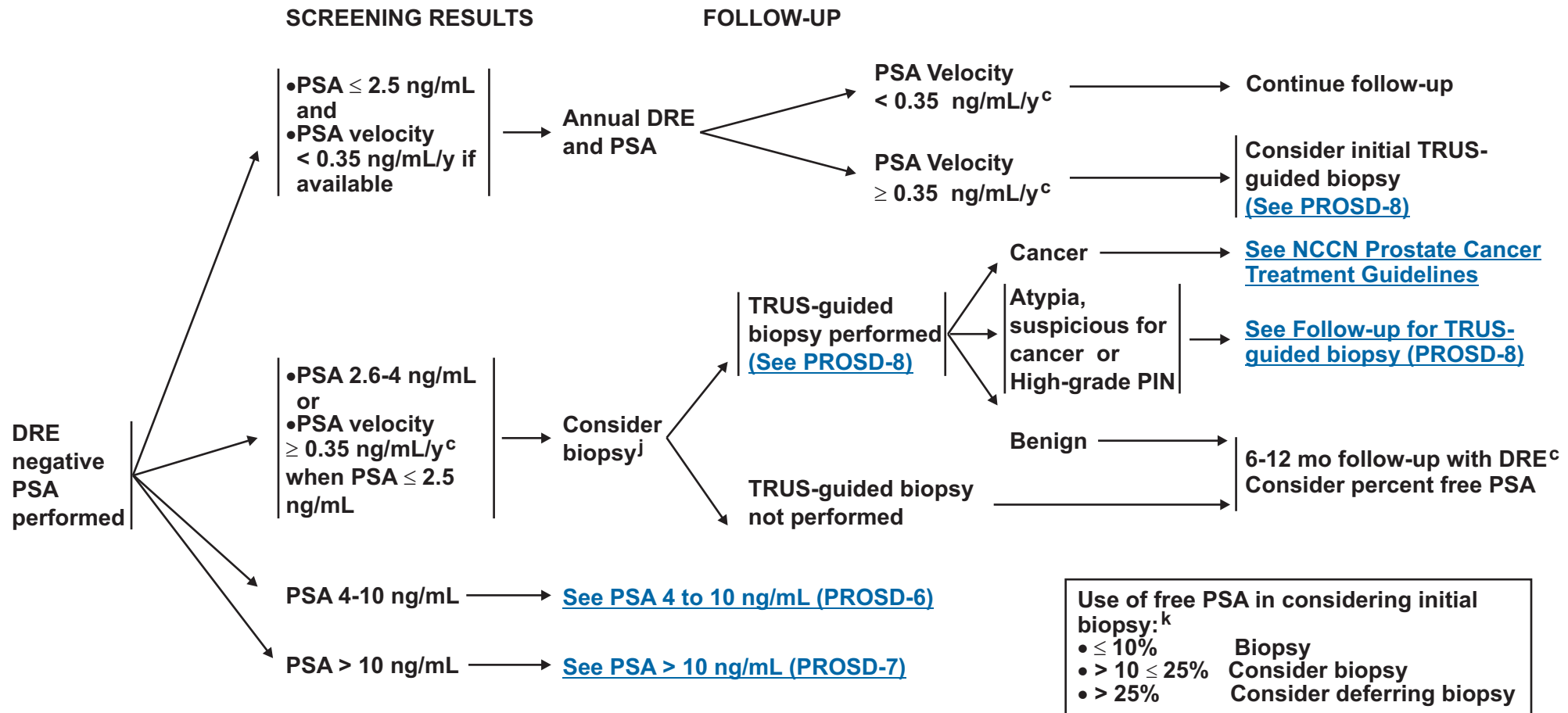
**PSA**

- Ejaculation:
  - ▶ Results are more reliable if patient has abstained from ejaculation for 48 hr. If this condition is not met, repeat after 48 hr abstinence, if the original sample was marginally elevated.
- Medicines that affect PSA:
  - ▶ Finasteride<sup>h</sup>
  - ▶ Androgen receptor blockers
  - ▶ Dutasteride<sup>h</sup>

<sup>h</sup>In patients using finasteride or dutasteride, failure to have a substantial decrease (approximately 50%) in PSA or an increase while on medication can be associated with an increased risk of prostate cancer.

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<sup>c</sup>PSA Velocity: For men with PSA  $< 4$  ng/mL, data suggest that a PSA velocity of  $\geq 0.35$  ng/mL/y is suspicious for the presence of cancer (Carter HB, Ferrucci L, Kettermann A et al. Detection of Life-Threatening Prostate Cancer With Prostate-Specific Antigen Velocity During a Window of Curability. J Natl Cancer Inst 2006;98(21):1521-1527) and biopsy is recommended; for men with PSA 4-10 ng/mL, a PSA velocity of  $\geq 0.75$  ng/mL/y is suspicious for cancer. PSA velocity in men with PSA  $> 10$  ng/mL is not available. Measurement should be made on at least three consecutive specimens drawn over at least an 18-24 mo interval. There is variability. Longer time periods increase reliability, but, as calculation of PSA velocity over longer prior time intervals usually decreases the PSA velocity estimate, it might decrease predictive power. It is also important to remember that biologic variability and/or prostatitis may be confounding factors in determining PSA velocity; therefore, antibiotic therapy and repeated PSA measurements should be used to minimize these sources of confusion.

<sup>j</sup> Factors to consider: age (men over 75 y should be considered individually), comorbid conditions, percent free PSA, prostate exam/size, strength of family history, African American.

<sup>k</sup> Free PSA is not generally used in deciding whether or not to perform an initial biopsy. However, in selected circumstances, it may be considered employing the following recommendations:  $> 25\%$ , no biopsy;  $\leq 10\%$  biopsy;  $> 10\% \leq 25\%$  indeterminate, consider biopsy.

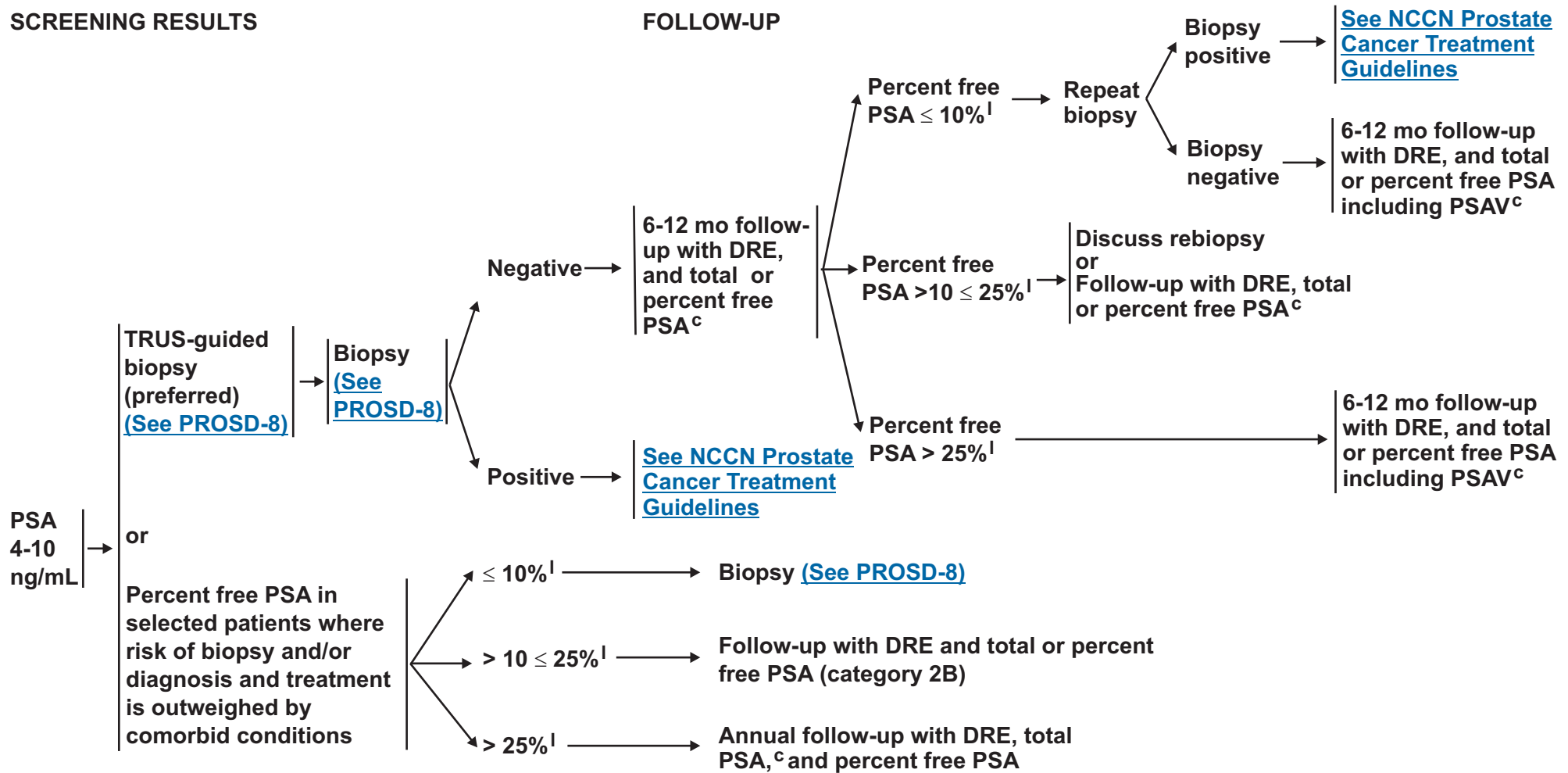
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# Prostate Cancer Early Detection

## SCREENING RESULTS

## FOLLOW-UP



<sup>o</sup>PSA Velocity: For men with PSA < 4 ng/mL, data suggest that a PSA velocity of  $\geq 0.35$  ng/mL/y is suspicious for the presence of cancer (Carter HB, Ferrucci L, Kettermann A et al. Detection of Life-Threatening Prostate Cancer With Prostate-Specific Antigen Velocity During a Window of Curability. J Natl Cancer Inst 2006;98(21):1521-1527) and biopsy is recommended; for men with PSA 4-10 ng/mL, a PSA velocity of  $\geq 0.75$  ng/mL/y is suspicious for cancer. PSA velocity in men with PSA > 10 ng/mL is not available. Measurement should be made on at least three consecutive specimens drawn over at least an 18-24 mo interval. There is variability. Longer time periods increase reliability, but, as calculation of PSA velocity over longer prior time intervals usually decreases the PSA velocity estimate, it might decrease predictive power. It is also important to remember that biologic variability and/or prostatitis may be confounding factors in determining PSA velocity; therefore, antibiotic therapy and repeated PSA measurements should be used to minimize these sources of confusion.

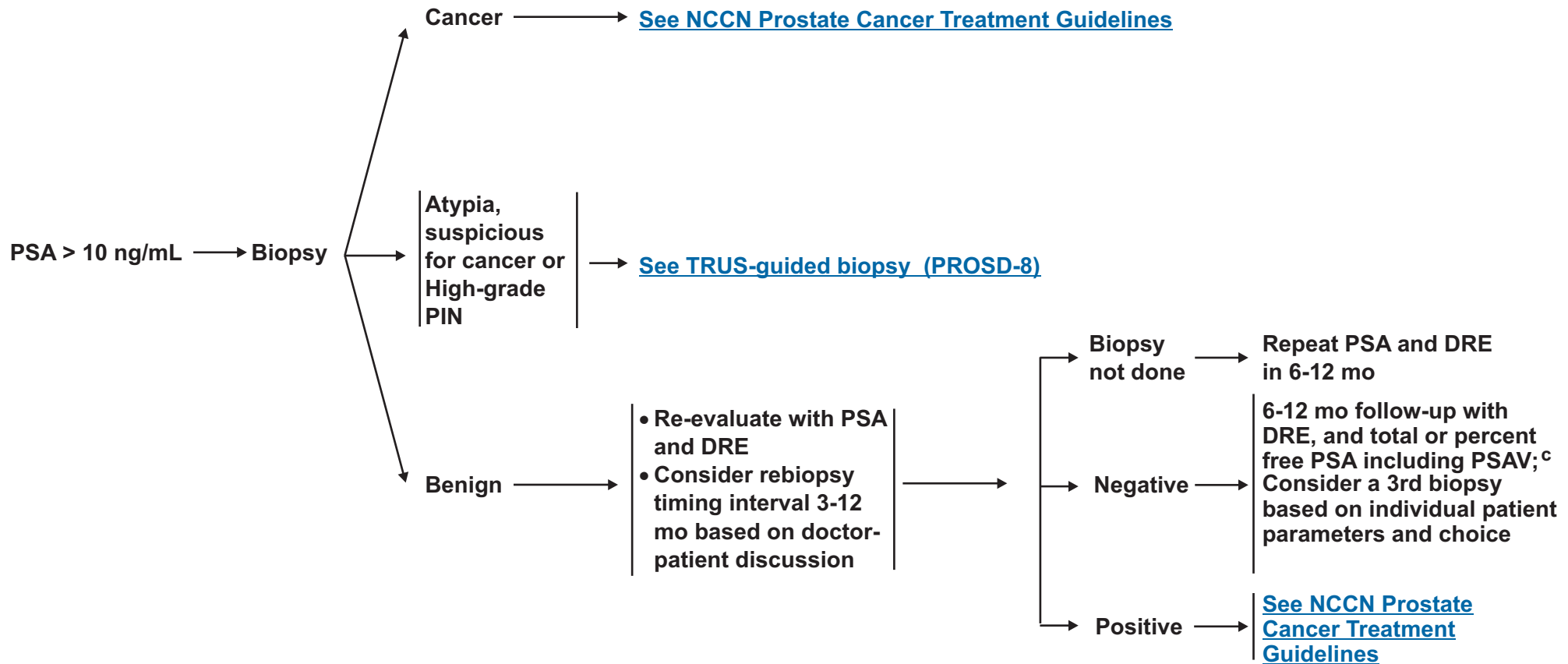
<sup>l</sup>Percent free PSA cut-off levels based on data from Catalona WJ, Partin AW, Slawin KM et al. Use of percentage of free prostate-specific antigen to enhance differentiation of prostate cancer and benign prostatic disease: a prospective multicenter trial. JAMA 1998; 279: 1542-7.

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**SCREENING RESULTS**

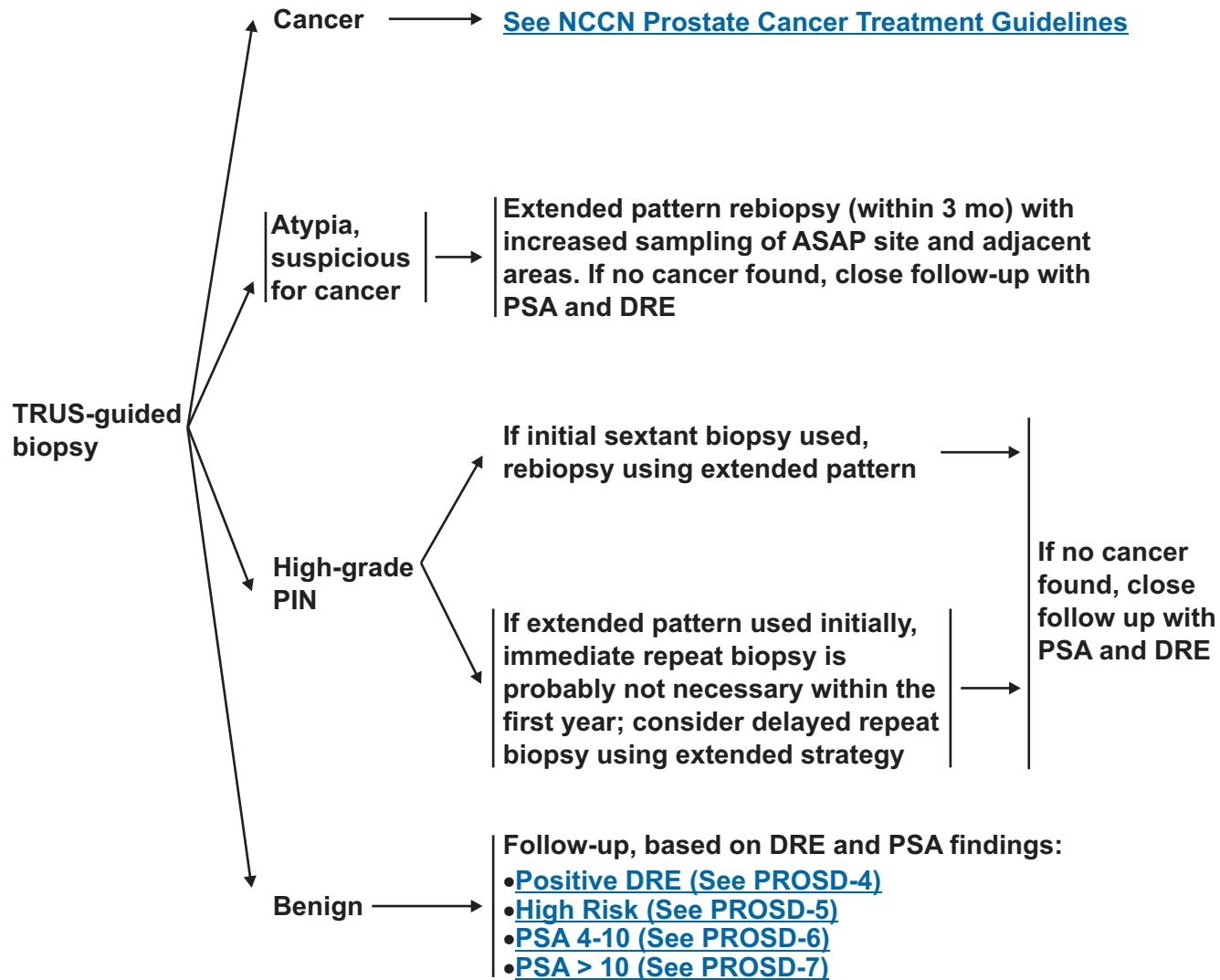
**FOLLOW-UP**



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**FOLLOW-UP FOR TRUS BIOPSIES**



**TRUS-GUIDED BIOPSY**

**Initial and Repeat  
Extended-pattern biopsy (12 cores)**

- **Number of Cores:**
  - › Sextant (6) and,
  - › Lateral peripheral zone (6) and,
  - › Lesion-directed at palpable nodule or suspicious image
- **Transition zone 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.**
- **For high risk men with multiple negative biopsies, consideration can be given to a saturation biopsy strategy.**
- **Local anesthesia can decrease pain/discomfort associated with prostate biopsy.**

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**SUGGESTED “TALKING POINTS” FOR DISCUSSION WITH A POTENTIAL SCREENER ABOUT THE PROS AND CONS OF PSA TESTING**

- Prostate cancer is the most common cancer found in older men, other than skin cancer.<sup>1</sup> Men in the United States have about 1 chance in 6 of eventually finding out they have prostate cancer.<sup>2</sup> Men who have regular PSA tests have a higher chance of finding out they have prostate cancer; men who do not have PSA tests have a lower chance but a higher probability of having more advanced cancer when ultimately diagnosed. The PSA test can detect the majority of prostate cancers earlier than a digital rectal examination when a man has no symptoms.
- African-American men and men with a father, brother, or son with prostate cancer (especially if it was found at a younger age) have a higher risk of prostate cancer. Native American and Asian-American men have a substantially lower risk.<sup>2</sup>
- American men also have about 1 chance in 30 of eventually dying from prostate cancer. However this would be higher, if no men opted for early detection and treatment. About 30,000 men die from prostate cancer each year in the United States. Only about 1 in 100 prostate cancer deaths occur in men under age 55. About 1 in 20 prostate cancer deaths occur in men age 55-64, 2 in 10 prostate cancer deaths occur in men age 65-74, and 7 in 10 prostate cancer deaths occur in men age 75 and older.<sup>2</sup> However, these deaths usually occur after some period of suffering from metastatic disease.
- Many prostate cancers grow very slowly. Consequently, many men with prostate cancer may die of something else before their prostate cancer causes any symptoms. However prostate cancers that grow more rapidly can potentially impact overall survival and quality of life. Whether a man will die of something else or prostate cancer depends on how aggressive the cancer is, how early it is detected, how effectively it is treated, as well as a man's age and his other medical problems. Most experts believe that in general men over age 75, or even younger men with serious medical problems, have little to gain from a PSA test.
- Doctors disagree about what level of PSA is high enough to do further testing, such as a prostate biopsy, to look for prostate cancer. Most doctors feel men with PSA levels greater than 4 should have a biopsy, while others feel men with levels greater than 2.5 should have a biopsy. There is an increasing tendency to focus less on absolute PSA values and to consider changes in PSA over time. There is accumulating evidence that men who have a steady rise in their PSA level are more likely to have cancer, and if the rise is rapid, the cancer is more likely to be life threatening. Other factors such as patient age and prostate volume (how large the gland is) are also important to consider when deciding who needs a prostate biopsy.
- A prostate biopsy is usually performed using local anesthesia through a probe placed into the rectum through which a needle is placed. This needle is used to take samples of the prostate tissue. Usually 10 to 12 samples are taken. The prostate biopsy, not the PSA test, tells whether or not a man has prostate cancer. A prostate biopsy is usually well tolerated and infrequently causes serious problems such as rectal or urinary hemorrhage, infection or urinary retention.
- A PSA test can be abnormal even when a man does not have prostate cancer. This is called a “false positive” test. These false positive PSA tests can come from other prostate conditions that are not important to find (unless a man has bothersome urinary symptoms). About 1 out of 3 men with a high PSA level have prostate cancer, which means that 2 out of 3 do not. The higher the PSA level, the more likely a man will be found to have prostate cancer if a biopsy is performed.<sup>3</sup>

[Talking Points continued on next page](#)

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**SUGGESTED “TALKING POINTS” FOR DISCUSSION WITH A POTENTIAL SCREENER ABOUT THE PROS AND CONS OF PSA TESTING**

- A PSA test can also be normal even when a man does have prostate cancer. This is called a “false negative” test. About 1 out of 7 men with PSA levels less than 4 have prostate cancer, which means 6 out of 7 do not.<sup>4</sup> The higher a man’s PSA level is across all PSA ranges from zero on up, the more likely a man is to have prostate cancer. This is true even within the so-called “normal” range below.<sup>4</sup>
- Prostate biopsies aren’t perfect tests, either. Prostate biopsies sometimes miss cancer when it’s there. Some doctors recommend a second set of biopsies if the first set is negative. Others will follow the PSA level and suggest more biopsies only if the level continues to go up.
- If prostate cancer is found after a PSA test and a biopsy, common treatments are surgery to remove the prostate or radiation treatment to the prostate. Surgery has a very small risk of death. Both radiation and surgery can cause problems with urinary leakage in some men, but the risk of urinary leakage is higher with surgery. Both radiation and surgery cause problems with getting and keeping an erection in many men. The risk of problems with erections is higher with surgery in the short run, but over the long run, the risk is about the same with the two treatments.<sup>3</sup> Radiation, though, also has a risk of causing bowel problems in some men. Some men, especially older men with slower-growing cancers, may not need treatments like surgery or radiation for their prostate cancer and can be followed with periodic PSA tests and physical exams, a process known as watchful waiting, active surveillance or expectant management.
- It is not clear if screening a man with the PSA test lowers his chances of eventually dying of prostate cancer or helps him live longer. It is also not clear if screening a man with the PSA test lowers a man’s chances of eventually having to deal with complications of prostate cancer, such as painful spread of prostate cancer to the bones, but the lower rates of advanced-stage disease at the time of diagnosis and the lower rates of prostate cancer deaths suggest that fewer men may suffer from advanced disease. As a result, doctors disagree over the value of screening men with the PSA test. However it is well established that screening has been associated with an unprecedented shift in the stages of prostate cancer at the time of diagnosis. More than 75 % of cancers are now detected when they are confined to the prostate gland, when current therapies are most effective. The actual relationship to PSA testing however remains unknown, but available evidence suggests that the lower mortality rates may be due, at least in part, to PSA testing. Special studies called randomized trials are the best way to determine how PSA testing affects the death rate from prostate cancer.
- Level 1 evidence for PSA screening is now available through a European study released in 2009. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in the early 1990’s to evaluate the effect of prostate-specific antigen (PSA) testing on death rates from prostate cancer. The trial involved 182,000 men between the ages of 50 and 74 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 162,243 men of ages of 55-69 years. Death from prostate cancer was the primary outcome. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. There were 214 prostate cancer deaths in the screening group, and 326 in the control group. The rate ratio for death from prostate cancer in the screening group, compared to the control group, was 0.80 (95% confidence interval [CI], 0.65-0.98; adjusted P=0.04). The researchers concluded that PSA-based screening reduced the rate of death from prostate cancer by 20%. However, they also concluded that this was associated with a high risk of over-diagnosis. Statistically, 1,410 men would need to be screened and 48 men would need to be treated to prevent one death from prostate cancer

[Talking Points continued on next page](#)

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## SUGGESTED “TALKING POINTS” FOR DISCUSSION WITH A POTENTIAL SCREENER ABOUT THE PROS AND CONS OF PSA TESTING

• In summary, there are advantages and disadvantages to having a PSA test, and there is no “right” answer about PSA testing for everyone. Each man should make an informed decision about whether the PSA test is right for him.

• **Frequency of biopsy complications with 10 core biopsy:**

- ▶ hematospermia - 37.4%
- ▶ hematuria greater than 1 day - 14.5%
- ▶ rectal bleeding < 2 days - 2.2%
- ▶ prostatitis- 1.0%
- ▶ fever > 38.5°C (101.3°F)- 0.8%
- ▶ epididymitis- 0.7%
- ▶ rectal bleeding > 2 days ± requiring surgical intervention- 0.7%
- ▶ urinary retention - 0.2%
- ▶ other complications requiring hospitalization- 0.3%

<sup>1</sup>Jemal A, et al. Cancer Statistics, 2006. CA Cancer J Clin 2006;56:106-130.

<sup>2</sup>Ries, et al (eds). SEER Cancer Statistics Review, 1975-2003, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2003/](http://seer.cancer.gov/csr/1975_2003/), based on November 2005 SEER data submission, posted to the SEER web site, 2006.

<sup>3</sup>Andriole GL, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005;97:433-8.

<sup>4</sup>Thompson IM, 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.

<sup>5</sup>Andriole GL, Reding D, Hayes RB, Prorok PC, JK; G. The prostate, lung, colon, and ovarian (PLCO) cancer screening trial: Status and promise. Urol Oncol. 2004;22(4):358-361.

<sup>6</sup>de Koning HJ, Auvinen A, Berenguer Sanchez A, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. Int J Cancer. 2002;97(2):237-244.

<sup>7</sup>Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000;21(6 suppl):273S-309S.

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## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

**Category 2A:** The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

**Category 2B:** The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

**Category 3:** The recommendation is based on any level of evidence but reflects major disagreement.

**All recommendations are category 2A unless otherwise noted.**

## Prostate Cancer Early Detection

The NCCN Prostate Cancer Early Detection Clinical Practice Guidelines in Oncology provide a set of sequential recommendations detailing a screening and subsequent work-up strategy for maximizing the detection of prostate cancer in an early, organ-confined state and attempting to minimize unnecessary procedures. It should be noted that these guidelines were developed for men who have elected to participate in prostate cancer screening; it is not meant to address the controversy regarding population screening.

### Overview

Prostate cancer is the most commonly diagnosed cancer in American men and the second leading cause of cancer deaths. More than 192,000 men will be diagnosed with prostate cancer in 2009, and an estimated 27,360 men will die of this disease.<sup>1</sup>

During the same period, nearly 20 million men in the United States will be confronted with important decisions regarding early detection for prostate cancer. Men in the United States have about one chance in six of eventually being diagnosed with this malignancy and about one chance in 30 of eventually dying of it.<sup>2</sup> African-American men and men with a first-degree relative with prostate cancer (especially cancer found at a younger age) have a higher risk of developing prostate cancer.<sup>2-4</sup> In a recent study of 26,111 men, the baseline PSA value is found to be a stronger predictive factor than a positive family history or being of African-American heritage.<sup>5</sup> Those men who undergo regular prostate-specific antigen (PSA) tests have a higher chance of undergoing prostate biopsy and of finding out if they have prostate cancer compared with men who do not undergo PSA tests. However, familial prostate cancers generally follow a more aggressive course, with higher grade and stage at diagnosis and increased risk of death from the disease.<sup>6</sup>

### Controversies on PSA testing

The decision about whether to pursue early detection of prostate cancer is complex. When, who and how to test remain a major debate topic among panelists. In brief, the dilemma is that because most men with prostate cancer will not die of this disease, treatment (often with significant side effects) is not necessary for some patients. Conversely, prostate cancer remains the second most common cause of male cancer deaths. Mortality related to prostate cancer depends on how aggressive the cancer is and the patient's age and comorbidities. Most experts believe that men over age 75 have little to gain from PSA testing, unless they have an aggressive tumor, in which case they may have substantial benefits. Unfortunately, there is currently no reliable method to distinguish between aggressive and slow-growing tumors.

Many would agree that the introduction of early detection methods such as DRE and the serum PSA test has played a critical role in the

downward migration of prostate cancer stage seen over the past decade. There has been substantial decrease in the rate of metastatic disease at the time of diagnosis since 1988.<sup>7,8</sup> Currently, 70% to 80% of prostate cancers are pathologically organ-confined at diagnosis.<sup>9</sup> Studies have shown that prostate cancer cases detected through PSA screening are more often confined to the prostate than those detected solely by DRE.<sup>10,11</sup>

Two large randomized trials initiated in the early 1990s have recently reported the impact of PSA screening on health outcome: the PLCO (Prostate, Lung, Colorectal, and Ovary) in the United States and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe. Interim reports have been released in 2009.<sup>12,13</sup> The ERSPC<sup>13</sup> involved 182,000 men between the ages of 50 and 74 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. There was an estimated 20% “contamination” (use of PSA tests) in the control. The predefined core group included 162,243 men of ages 55-69 years. Death from prostate cancer was the primary outcome. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group versus 4.8% in the control group. There were 214 prostate cancer deaths in the screening group compared to 326 in the control. The rate ratio for death from prostate cancer was 0.80 for the screening arm as compared to control (95% CI, 0.65-0.98; adjusted P=0.04). The investigators concluded that the PSA-based screening program reduced mortality from prostate cancer by 20%. However, they also noted that this was associated with a high risk of over-diagnosis. Statistically, 1,410 men would need to be screened and 48 additional men would need to be treated to prevent one death from this malignancy. The NCCN panel considers this report high level evidence, although the follow-up time is relatively short for definitive conclusions. Future updates on this trial will provide more information.

The PLCO study<sup>12</sup> randomized 76,693 men at 10 U.S. study centers to annual screening (annual PSA for 6 years and DRE for 4 years) or usual care. After 7 years of follow-up, the incidence rate ratio for the screening arm compared to control was 1.22 (95% CI, 1.16-1.29). The investigators did not find a statistically significant difference between the mortality rates of the screening group (50 deaths, 2.0 per 10,000) and of the control (44 deaths, 1.7 per 10,000). Despite the impressive sample size, the report is heavily flawed by the short follow-up time and the unusually high contamination rate of 40-52% in the control. Improvement in mortality by PSA testing is likely a long-term outcome evident only with longer follow-up

In light of these results, panelists raised several points. First, the ERSPC study outlined a beneficial, but not necessarily exclusive, scheme in using PSA testing to prevent deaths by prostate cancer (testing men between ages 50 and 74 every 4 years). Second, PSA testing is likely optimal when used for early detection in high-risk populations instead of general screening. Focusing on rigorous early detection in young men of African descent or with a strong family history of prostate cancer (first degree relative with prostate cancer, especially at a young age) may be the key to improving the survival rate of this malignancy. Unfortunately, neither study addressed high risk factors, with less than 5% of PLCO participants of African-American descent and only 7% with a reported family history.<sup>12</sup> Third, panelists agreed that age is an important factor for consideration. Young men who belong to a high risk group have a heightened chance of dying of prostate cancer and will thus benefit from early testing. For older men, more judicious use and interpretation of the PSA test is warranted to prevent over-detection.

### PSA Test and Its Derivatives

When the first recommendations for early detection programs for prostate cancer were made, serum total PSA was the only PSA-based

test available. Subsequent years have seen the development of an exciting series of PSA derivatives that are possibly useful in increasing specificity and decreasing unnecessary biopsies.

#### **Total PSA (tPSA)**

The development of PSA testing is arguably the most important advance that has been made in detecting prostate cancer at an early stage. 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 "leaks" into the circulation by means of an unknown mechanism. Many commercially available sources of PSA antibodies for serum tests are now available worldwide. With the exception of minor differences in the calibration of these assays, they perform comparably when used appropriately. However, the levels are not interchangeable since they are standardized against two different standards. The test should be repeated if increased levels are noted, particularly if the value is close to the threshold.

#### *Effect of medication and herbal supplements on total PSA*

The effect of the 5-alpha reductase inhibitors finasteride and dutasteride on serum PSA levels has been well documented in several studies. This class of drugs typically results in an approximate 50% decrease in serum PSA levels after 6 to 12 months. However, this effect is tremendously variable. For example, one study showed that at 1 year, only 35% of men had the expected 40% to 60% decrease in PSA and another 30% had greater than a 60% decrease in serum PSA levels.<sup>14</sup> Thus, not only should care be taken to elicit the use and duration of use of 5-alpha reductase inhibitors during history taking, but the commonly employed "rule of thumb" to simply double the measured PSA value may result in unreliable cancer detection.

A health survey on 12,457 men visiting a prostate cancer screening clinic showed that over 20% men take herbal supplements, while only

10% take prescription medication (such as finasteride) for lower urinary tract symptoms.<sup>15</sup> 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.

#### *Total PSA thresholds*

Numerous studies have shown that a PSA level above 4 ng/mL increases the chance of detecting prostate cancer at prostate biopsy to nearly 30% to 35%. Large programs for the early detection of prostate cancer have shown that nearly 70% of cancer cases can be detected using a PSA cutoff level of 4 ng/mL in the first four years.<sup>16</sup> Overall, appropriate use of PSA alone can provide a diagnostic lead time of nearly 5 to 10 years compared with DRE. More than 90% of PSA-detected cancers are biologically significant based on tumor volume and tumor grade criteria.<sup>16</sup> PSA examination results in detection of earlier, organ-confined disease.<sup>10,11,17</sup> Recent studies have investigated the predictive value of evaluating men with PSA values in the 2.5 to 4.0 ng/mL range (see subsequent sections).

#### **PSA Velocity**

The rate of change in PSA over time is called the PSA velocity (PSAV). This parameter was first introduced by Carter et al.<sup>18</sup> This study showed for the first time that the "rate of change" of serum PSA over time provides useful information and increases the specificity of PSA for cancer detection. These authors showed that a cutoff of 0.75 ng/mL/y had a sensitivity of 79% among men with cancer and a specificity of about 90% among those without cancer when PSA levels were between 4-10 ng/ml. When PSA levels were less than 4ng/ml, sensitivity using a cutoff of 0.75 ng/ml was only 11% but more recent studies from the same group demonstrated that PSAV over 0.35 ng/ml/y<sup>19</sup> and a high risk count (number of times the PSAV exceeds a

threshold)<sup>20</sup> 10 to 20 years before diagnosis predict high-risk prostate cancer. Among men with prostate cancer, high PSAV (over 2 ng/ml/y) during the year before diagnosis is also associated with an increased risk of death from the disease.<sup>21</sup> It should be noted that the predictive value of PSAV can be influenced by other factors such as absolute PSA level.<sup>21-23</sup>

PSA velocity measurements can be confounded by prostatitis, a condition that can cause dramatic increases in PSA levels.<sup>24</sup> In fact, men with very high PSA velocities are more likely to have prostatitis than prostate cancer. Therefore, it is helpful to try to rule out prostatitis by diagnostic evaluation and empiric antibiotic therapy.<sup>25</sup> Currently, PSA velocity has been best used in younger men who have elected to begin early detection programs before age 50. Men in this age group seldom have enough prostate enlargement to confound the interpretation of PSA.

#### **Age- and Race-Specific PSA Reference Ranges**

Age-specific PSA reference ranges were introduced by Oesterling and colleagues as a method to increase cancer detection (increase sensitivity) in younger men by lowering their PSA cutoff values and to decrease unnecessary biopsies (improve specificity) in older men by increasing their PSA cutoffs.<sup>26-28</sup> These age-specific ranges have been investigated by several groups with equivocal results. Race-specific reference ranges have also been suggested.<sup>29</sup> However, the exact roles of these age- and race-specific PSA cutoffs in the early detection of prostate cancer remain unclear and continue to be the source of debate. The panel, therefore, chose not to incorporate these variables into the current guidelines.

#### **Percent-free PSA (fPSA)**

A flurry of exciting work over the past decade has characterized a family of molecular forms of PSA and their possible clinical roles. Free (unbound) PSA expressed as a ratio of total PSA has emerged as a

clinically useful molecular form of PSA, with the potential to provide improvements in 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% to 90%) of circulating PSA is covalently bound to endogenous protease inhibitors. Most immunoreactive PSA is bound to a protease inhibitor called 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 free PSA is significantly lower in men who have prostate cancer compared with men who do not.

The US Food and Drug Administration (FDA) approved the use of percent-free PSA for the early detection of prostate cancer in men with PSA levels between 4 and 10 ng/mL. The multi-institutional study that characterized the clinical utility of this assay showed that a 25% free PSA cutoff detected 95% of prostate cancers while avoiding 20% of unnecessary prostate biopsies.<sup>30</sup> Since its approval by the FDA, testing for percent-free PSA has gained widespread clinical acceptance in the United States, specifically for patients with normal DREs who have previously undergone prostate biopsy because they had a total PSA level within the "diagnostic gray zone" (ie, between 4 and 10 ng/mL).

**Complexed PSA (cPSA)**

As noted previously, PSA exists in both free and several complexed forms. Direct measurement of the complexed form with alpha-1-antichymotrypsin is now available. For practical purposes, total PSA consists essentially of free PSA and the alpha-1-antichymotrypsin complexed form. The threshold levels are therefore not equivalent: cPSA levels of 2.2 and 3.4 ng/mL are equivalent to tPSA levels of 2.5 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.<sup>31</sup> Results were similar for percent cPSA and percent fPSA. Therefore, the ratio of complexed to total PSA should provide comparable information as the free to total PSA ratio.<sup>32</sup> Other studies also demonstrated an enhanced specificity of cPSA within certain tPSA ranges.<sup>33-35</sup> 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.

**PSA Density**

Prostate-specific antigen density requires the measurement of prostate volume by transrectal ultrasound (TRUS) and is expressed as the PSA value (in nanograms per milliliter) divided by the prostate volume (in cubic centimeters). Benson and coworkers<sup>36</sup> first proposed the use of PSA density as a means of discriminating prostate cancer from the most frequent cause of PSA elevation, benign prostatic hypertrophy. Initially, PSA density was used to differentiate high PSA levels in men with large prostates who did not have prostate cancer. A PSA density cutoff of 0.15 mg/mL/cc was recommended in earlier studies, which spared as many as 50% of these patients from undergoing unnecessary biopsies. However, some subsequent studies have reported that the 0.15 cutoff has insufficient sensitivity.<sup>37</sup>

More recent studies have tried to improve upon the performance of PSA density by using complexed<sup>38</sup> or free PSA<sup>39</sup> in the numerator or correcting the denominator for transition zone volume.<sup>40</sup> The lack of precision of measurement of both PSA and prostate volume has prevented the widespread clinical acceptance of PSA density. In addition, studies have shown that percent-free PSA provides comparable results as PSA density in early-detection algorithms.<sup>41</sup> While the panel recognizes that PSA density may explain an elevated PSA value considered after negative biopsies, it is not incorporated into the early detection guidelines because it offers little added benefit over other tests. However, PSA density has been clinically under-utilized and may be considered in evaluating patients, especially those who have had prior ultrasound-determined measurements of prostate volume. PSA density has been shown to correlate with prostate cancer presence and aggressiveness, and can predict adverse pathology and biochemical progression after treatment.<sup>42,43</sup>

**Age at Onset of Screening**

Although age 50 has traditionally been the age for starting to consider PSA screening, researchers have recognized that high-risk groups such as African-Americans and men with family histories of prostate cancer may benefit from beginning screening at an earlier age.

The Baltimore Longitudinal Study on Aging identified median PSA levels as a function of age; the median PSA is 0.6 ng/mL for men in their 40s and 0.7 ng/mL for men in their 50s. Significantly, they found a threefold higher risk of prostate cancer within 10 to 25 years if PSA was greater than the median for the patient's age group.<sup>44</sup> For patients screened in their 50s, a baseline PSA value between the age-specific median and 2.5 ng/mL was associated with a 7.6-fold higher risk of prostate cancer.<sup>45</sup> Autopsy studies have shown that histologic evidence of prostate cancer is present in approximately 25% of men in the fourth decade of life, and the Surveillance Epidemiology and End Results

(SEER) Database shows that prostate cancer deaths begin to appear in men in their 40s.<sup>2</sup> Accordingly, to prevent these tragic, untimely deaths, screening for prostate cancer should begin earlier. In addition, PSA values in the 40s are less influenced by possible presence of significant benign prostatic hyperplasia (BPH). It seems reasonable to obtain a baseline PSA test at age 40 to assess the risk for subsequent prostate cancer detection. This risk assessment might be useful in determining the most appropriate surveillance strategy for the individual, as well as whether or when a prostate biopsy should be recommended. However, several panelists have also expressed doubts on the cost-effectiveness and concerns on potential over-diagnosis of universal testing at age 40. Nonetheless, there is uniform agreement that an early screening program will likely benefit young men in a predefined high risk group (African descent, family history).

#### **Threshold for Prostatic Biopsy**

A total PSA level of 4.0 ng/mL has traditionally been used as the threshold for consideration of a prostate biopsy, recognizing that 30% to 35% of men in the 4 to 10 ng/mL range will be found to have cancer. Subsequent studies have shown that a substantial number of men with a PSA level between 2.5 and 4.0 ng/mL will have cancer. A study of 332 screened men with PSA in this range revealed a 22% incidence of prostate cancer by biopsy.<sup>46</sup> A prospective study of 151 subjects with PSA values in this range showed an incidence of 24.5%.<sup>47</sup> These cancers are comparable to those found with higher PSA levels in terms of clinical significance based on the volume and Gleason score, but are more frequently organ-confined.<sup>48,49</sup> Researchers have estimated that lowering the threshold to 2.6 ng/mL would double the rate of detecting cancer in men younger than 60 years old with little loss of specificity.<sup>50</sup>

The Prostate Cancer Prevention Trial (PCPT) demonstrated that 15% of men with a PSA level of 4.0 ng/ml or less and a normal DRE had prostate cancer diagnosed on end-of-study biopsies.<sup>51</sup> There was a

direct correlation between the PSA level and the prostate cancer detection rate, ranging up to 26.9% in patients whose PSA was 3.1 to 4.0 ng/ml. High-grade prostate cancers (defined by a Gleason score of 7 or greater) was prevalent in 25% of patients with a PSA level of 3.1 – 4.0 ng/mL. Thus high-grade prostate cancers detected by biopsy are not rare among men with PSA levels of 4.0 ng/mL or less.

Based on this and other supportive data, it now appears that the use of a PSA threshold of 4.0 ng/mL will miss a significant number of potentially curable tumors. The NCCN guidelines therefore recommend consideration of biopsies for men with PSAs in the range of 2.6 to 4.0 ng/mL. The caveat remains, of course, that the definitive demonstration of improvement in mortality from PSA screening still awaits the results of ongoing, large randomized trials and considerations of quality of life.

## **NCCN Guidelines**

### **General Considerations**

The decision to participate in an early detection program for prostate cancer is complex for both the patient and physician. Important factors that must be considered when beginning an early-detection program include patient age, life expectancy, family history, race, 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, and life expectancy of the patient are paramount when recommending or designing an early detection program.
- Prostate cancer risk factors, such as family history and race (i.e., African-American), must be considered before decisions concerning the initiation of an early detection program are made.
- Prostate cancer in its early stages has no identifiable symptoms. In advanced disease, symptoms may include urinary obstruction, prostatic bleeding, hematospermia, and bone pain. Although most men wishing to take part in early detection programs have no symptoms of prostate cancer, they may have mild to severe symptoms of lower urinary tract disease because of benign prostatic enlargement. Care should be taken to educate patients about the distinction between these two diseases when discussing the risks and benefits associated with early detection.
- A patient's history of prior testing, including DRE, PSA, PSA derivatives, and prostate biopsy, must be considered when designing an early detection program for that patient. Patients who have had numerous serial PSA values should make the information available to the physician. In addition, previous negative prostate biopsy results and the actual histologic findings should also be made available. Although a clear understanding of the approach to early detection in men who have a long history of abnormal PSA values has not been completely documented, these earlier test results should be considered when testing intervals are chosen.
- Numerous large, community-based early detection programs have clearly documented the synergy of DRE and PSA testing

in increasing the sensitivity for the detection of prostate cancer over the use of either test alone. Serum PSA testing is not a substitute for a thorough DRE.

- Total PSA levels greater than 10 ng/mL confer a greater than 67% likelihood of harboring prostate cancer. Thus, men with serum PSA values over this level (regardless of their DRE results, percent-free PSA, or PSA velocity values) should undergo a TRUS-guided biopsy of the prostate. False-negative findings should be discussed clearly with the patient and a repeat biopsy considered if total PSA values continue to remain in the high-risk category.

### Specific Considerations

A thorough discussion on the pros and cons of screening must be carried out between the physician and the potential participant (see [PROSD-A](#)).

Studies have shown that among the general population of men in their 40s, baseline PSA level is predictive of diagnosis of prostate cancer many years later.<sup>45,52</sup> Hence for men opting to participate in an early detection program, baseline DRE and PSA testing at age 40 is useful. Annual follow-up is recommended for men who have a PSA value  $\geq 1.0$  ng/ml. Men with PSA below 1.0 ng/ml should be screened again at age 45. These recommendations have a majority, but not uniform, panel consensus for men of average risk (category 2B). Regular screening should be offered to all participants starting at age 50.

Men of African-American descent and men with a first-degree relative diagnosed with prostate cancer (especially at a young age) have a significantly higher risk.<sup>2-4</sup> For these men, panelists agreed that earlier (start in the 40s) and more frequent screening is appropriate. Panelists also agree that screening and biopsy decisions should be individualized for men over 75; less frequent PSA/DRE may be reasonable for older

patients. This is supported by a recent longitudinal study of 849 men that found no prostate cancer deaths among age 75-80 men with PSA levels below 3.0 ng/mL.<sup>53</sup>

## Prostate Biopsy

### *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 aspect 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 in a large study of 2299 patients involving 167 community-based Urologists.<sup>54</sup> The overall cancer detection rate in this referral-based population was 44%. If only a sextant scheme was performed, approximately 20% of the cancers in the series would have been missed. Lesion-directed biopsies (hypoechoic lesions seen on TRUS) rarely contribute to unique cancer identification not detected by extended systematic biopsy. The utility of transition zone biopsies in initial biopsy patients is low and is not recommended.<sup>55,56</sup>

The panel recommends an extended-pattern 12-core biopsy [sextant (6) and lateral peripheral zone (6) and lesion-directed palpable nodule or suspicious image]. Transition zone 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.

### *Repeat Biopsy Technique*

Patients with prior negative biopsies, yet persistently rising PSA values should undergo repeat biopsy. Important factors in predicting chance of cancer on repeat biopsy include PSA velocity and the adequacy of initial biopsy (number of cores, prostate size). Cancer detection rates are higher in men with prior negative sextant biopsies compared to those with prior negative extended biopsies. Yields are highest in the laterally directed cores and the apical cores.<sup>57</sup> Particular attention should be given to apical sampling including the anterior apical horn, which is comprised of peripheral zone.<sup>58</sup> Transition zone biopsies can be considered in repeat biopsy patients. In patients with two negative extended biopsies, yet persistently rising PSA values, a saturation biopsy may be considered.<sup>59</sup>

### *Use of anesthesia*

Historically, up to 90% of men undergoing a prostate biopsy have reported some discomfort during the procedure.<sup>60</sup> Both topical lidocaine gel and an injectable nerve block have been shown to be safe and efficacious in reducing discomfort.<sup>61</sup> Topical lidocaine was more efficacious in reducing pain during probe insertion, whereas periprostatic 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.<sup>62</sup> For exceptional cases such as men with anal strictures or patients who have been inadequately blocked with a periprostatic injection, intravenous sedation or general anesthetic may be advantageous.

### *Percent-free PSA*

The NCCN guidelines recommend the use of the percent-free as an alternative in the management of patients with normal DREs and total PSA levels between 4-10 ng/mL if there is a contraindication to biopsy. Physicians and patients electing to use percent-free PSA should be cautioned that this assay and the multi-institution study performed to

obtain its FDA approval were designed with the intention of avoiding unnecessary biopsies in men with a high likelihood of not having prostate cancer. If an anticoagulated patient presents with a negative DRE, total PSA value of 4-10 ng/mL, and percent-free PSA levels greater than 25% annual follow-up with DRE, tPSA, and percent free PSA can be considered.<sup>63</sup> This strategy met with less-consensus (category 2B) if the percent free PSA is greater than 10% and 25% or less, where biopsy is preferred.

Percent-free PSA levels less than 10% are clearly associated with a high risk of having prostate cancer, and patients should be encouraged to undergo a biopsy if percent-free PSA values fall below this level. There is a negative linear relationship between the likelihood of having prostate cancer and having percent-free PSA values between the levels of 10% and 25%. The risks associated with these values should be carefully discussed with the patient before electing to forego prostate biopsy. In general, percent-free PSA is used in the decision process when an individual has had an initial negative biopsy.

In addition, physicians should consult the clinical chemistry laboratory to determine manufacturer's recommendations regarding sample collection and sample handling. It should also be noted that "mixing and matching" free and total PSA assays from different manufacturers is not recommended and may lead to spurious results.

#### ***PSA velocity***

Initial studies of PSA velocity have determined that an increase in the serum PSA levels  $\geq 0.5$  ng/mL/y indicates a high likelihood of having prostate cancer. A study on 980 men by Carter et al<sup>19</sup> suggested that a PSAV of greater than or equal to 0.35 ng/ml/y is suspicious of cancer and biopsy is recommended. However, the small number of deaths from prostate cancer (20) in the study precludes definitive conclusions. There is debate over whether a velocity of 0.35 ng/mL/y is a reliable criterion for recommending biopsy when the PSA level is low.

Carter and colleagues have described the technique for calculating PSA velocity in detail.<sup>18,19</sup> The PSA values used to calculate PSA velocity should be performed by similar assay techniques in the same clinical laboratory. PSA velocity should be calculated from at least three consecutive PSA values obtained over at least an 18-24 month period. Longer time periods increase reliability. In patients using finasteride or dutasteride, failure to have a substantial decrease in PSA or an increase indicates that they are at increased risk for prostate cancer.

The research that went into the determination of PSA velocity cutoff points was collected primarily in men with PSA levels less than or equal to 10 ng/mL. A recent screening study reported that PSA velocity is not useful in for cancer detection or prognostic prediction for men with PSA levels greater than 10 ng/mL.<sup>64</sup> However, guideline panel members universally endorse performing a prostate biopsy in all men with a PSA value greater than 10 ng/mL who also fulfill other screening criteria. Patients and physicians electing to monitor prostate disease by measuring PSA velocity should be cautioned that fluctuations between measurements can occur as a result of either laboratory variability related to inter-assay variability from the use of different commercially available sources or from individual biologic variability. Prostatitis may also cause PSA velocity to rise. Antibiotic therapy and repeated measurements may be considered to minimize these confounding factors.

#### ***Management of Negative or Suspicious Biopsies***

Increasingly, pathologists have recognized the importance of reporting non-malignant but pathologically atypical findings. High grade prostatic intraepithelial neoplasia and atypical small acinar proliferation are noted in up to 14% and 3% of biopsies, respectively.<sup>65,66</sup> Such diagnoses are often confirmed through the use of immunohistochemical staining for basal cell markers and markers of neoplasia such as Alpha Methyl-Acyl CoA Racemase (AMACR).<sup>67,68</sup>

*High-grade Prostatic Intraepithelial Neoplasia (HGPIN).* Cytologically, the nuclear features of HGPIN resemble that of cancer; however the presence of a basal layer on the acini distinguishes this entity from cancer. Extended biopsy schemes have dramatically resulted in a decline in the positive re-biopsy rate in patients initially found to have HGPIN. While reports in the sextant biopsy scheme era demonstrated positive re-biopsy rates of approximately 50%, contemporary series using extended biopsy schemes report positive re-biopsy rates of approximately 10-20%.<sup>69,70</sup>

*Atypia, suspicious for cancer.* Distinct from HGPIN in which a basal cell layer is present, atypia is characterized by small single-cell layer acini. However, 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, positive re-biopsy rates in patients with atypia are 50% or more and the most likely area of finding cancer resides in the prostate area demonstrating atypia.<sup>71,72</sup> Hence a repeat extended biopsy scheme is warranted with additional cores being obtained from the prior region demonstrating atypia.

If the biopsy result for a man with PSA level greater than 10 ng/mL reveals histologic evidence of atypia or high-grade PIN (prostate intraepithelial neoplasia) TRUS-guided biopsy is indicated. The NCCN guidelines therefore recommend that if high-grade PIN is found on TRUS-guided biopsy, of less than 10 cores, repeat biopsy using an extended pattern, including transition zone, is indicated if an extended biopsy strategy was not used. If extended biopsies were used, a delayed strategy (1 year after the extended biopsy) may be considered, as suggested by Lefkowitz et al.<sup>73</sup> For findings of atypia, suspicious of cancer, extended pattern re-biopsy (within 3 months) with increased sampling of atypia site and adjacent areas is recommended.

*Negative biopsy in the absence of suspicious lesions.* Men with a PSA of 4 to 10 ng/mL with a percent fPSA level less than or equal to 10%

should undergo a repeat biopsy. If the fPSA level is greater than 10% and less than or equal to 25%, repeat biopsy or close follow-up with tPSA or percent fPSA (category 2B) can be considered. If the fPSA is greater than 25%, the surveillance strategy (6-12 month follow-up with DRE, tPSA and percent fPSA) can be used.

If a biopsy returns as negative in a man with a serum PSA level greater than 10 ng/mL, DRE and PSA testing should be repeated, and a repeat prostate biopsy should likewise be considered at 3-12 month interval based on discussion with the patient. Given the importance of technique, issues discussed above regarding the use of extended or saturation techniques for a repeat prostate biopsy should be considered.

## Summary

Since the early 1990s, many variants of the total PSA assay have been introduced in attempts to increase the sensitivity of screening programs (cancer detection) while maintaining specificity (elimination of unnecessary biopsies). Again, it is important to note that 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 Prostate Cancer Guidelines](#)).

The NCCN guidelines incorporate many new validated findings in addition to the DRE and tPSA test. These new factors include percent-free PSA, PSA velocity, complexed PSA, biopsy pathology, and TRUS-guided biopsy techniques. The panel will re-examine the

clinical utility of these 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 the NCCN and this guideline panel in updating these algorithms is that they will assist men and clinicians choose 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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