Biomarkers in Prostate Cancer

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Abstract

Prostate cancer represents the most common noncutaneous cancer in men in the United States. Although PSA testing with or without digital exam has led to increased prostate cancer detection, it continues to lack specificity, which leads to the inability to predict which men will benefit from biopsy and/or prostate cancer treatment. The lack of specificity has led to varying screening recommendation from multiple organizations. Patients are also questioning the benefit of PSA screening. This article reviews the history of prostate cancer and PSA screening, discusses the current controversy in PSA screening, and provides guidelines for the role the advanced practitioner in patient selection and counseling. The continual controversy has led to more interest in pursuing more accurate predictors of prostate cancer. A discussion of emerging biomarkers, *PCA3*, and the *TMPRSS2:ERG* gene is also included.

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Prostate cancer is the most common malignancy among all races of men and the second leading cause of cancer-specific death in men in the United States (Centers for Disease Control [CDC], 2006). It is estimated that one in six men will be diagnosed with prostate cancer in his lifetime (United States Preventive Services Task Force [USPSTF], 2010). The median age of death from prostate cancer is 80 years and 71% of men die after age 75 (USPSTF, 2010); 63% of men age 65 and older are diagnosed with prostate cancer (NCI, 2009). African American men have twice the rate of occurrence as their Caucasian counterparts (USPSTF, 2010).

Risk factors for prostate cancer include African American race, family history, age, and possibly diet. Diets high in animal fat have been linked to prostate cancer (National Cancer Institute [NCI], 2009). Prostate cancer–specific mortality in the United States has greatly decreased (approximately 33%) because of the widespread use of prostate-specific antigen (PSA) screening (Botchorishvili, Matikainen, & Lilja, 2009).

Prostate cancer prognosis is related to many factors, including histologic tumor grade, patient age, comorbidities, and PSA level. However, the most important factor is tumor stage at diagnosis (NCI, 2010). More than 90% of all prostate cancers are diagnosed

at a localized stage. Diagnosis at the local stages has resulted in a 5-year survival rate approaching 100%, which is an increase from 69% since 1975 (Shao et al., 2010). This improvement has been attributed to early detection and subsequent treatment following elevated PSA results. There are several pieces of information that need to be considered when assessing whether a man has prostate cancer: PSA, digital rectal exam (DRE), comorbidities, and other risk factors. Generally, prostate cancer is asymptomatic until it becomes advanced disease. Symptoms such as dysuria, urinary retention, hematuria, inguinal adenopathy, and bone pain are generally only present after the tumor has progressed to more advanced stages.

History of PSA in Prostate Cancer

Prostate-specific antigen, which is produced by the prostate gland, was first described as a marker for human semen in forensics (Loeb & Catalona, 2010), and it was considered prostate-specific but not prostate cancer–specific. Elevations may be due to an enlarged prostate, infection, inflammation, age, or race (American Urological Association [AUA], 2009). Before 1986, the digital rectal exam was the only screening test available for prostate cancer and positive results were generally associated with late-stage disease. Prostate-specific antigen was approved by the US Food and Drug Administration as a test to monitor prostate cancer progression in 1986. Prostate-specific antigen became widely used for cancer screening in the 1990s, with a subsequent increase in diagnosis of prostate cancer peaking in 1992 (Hoffman, 2010). A 1995 study by Gann et al. showed that PSA levels were closely associated with prostate cancer (Gann, 1995).

Prostate-specific antigen belongs to the human kallikrein family of proteins, is regulated by androgen secretion, and has many uses in clinical practice. Early detection of prostate cancer, clinical staging, prognosis, tumor recurrence, and assessment of therapeutic response to androgen suppression, radiation, and chemotherapy are all roles for PSA (Lieberman, 2004).

There has been a significant reduction in mortality in prostate cancer patients since the increased use of PSA in 1996 (Lieberman, 2004). Prostatic acid phosphatase was used as a prostate tumor marker in the past, but it was only useful for advanced malignancies and did not successfully identify localized tumors. Studies in the recent past have indicated that men with levels of PSA within the reference range for normal may actually have prostate cancer. Therefore, further research is needed to determine (1) the specific PSA levels that determine a man's risk of prostate cancer and (2) the survival benefit of PSA screening (Ilic, O'Connor, Green, & Wilt, 2008).

Use of PSA in Prostate Cancer Screening

Screening in any form is generally used to reduce the risk of mortality as well as improve patients' quality of life. Despite multiple studies, there continues to be a lack of consensus on how to best use PSA as a screening tool or tumor marker. Because PSA is not conclusive, other tests such as ultrasound, biopsy, or cystoscopy are indicated if PSA or DRE suggests cancer. Men that have abnormal prostate exams or suspicious PSA levels should be referred to a urologist for an evaluation. There are two trials currently underway that may aid in the decision to use PSA: the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; Ilic et al., 2008). These will be addressed in detail later in this article.

The American Urological Association recommends PSA screening for men that have at least a 10-year life expectancy and are having voiding symptoms (AUA, 2009); an increased PSA may aid in urologic management decision-making. The American Cancer Society recommends yearly PSA and digital rectal exams for men with a life expectancy greater than 10 years beginning at age 50 (ACS, 2010). Men with high risk factors (black men, family history of diagnosis before age 65 years, known or likely *BRCA1* or *BRCA2* mutations) for prostate cancer should begin at age 40 through 45 (Hoffman, 2010). The United States Preventative Services Task Force does not have a recommendation for routine screening for prostate cancer because it has been determined that there is insufficient evidence to balance the benefits vs. harms associated with screening. They do recommend against screening men age 75 and older for prostate cancer (USPSTF, 2010).

The sensitivity of PSA has been determined to be between 70% and 80% and specificity is estimated to be between 60% and 70%, with a posi-

tive predictive value for PSA levels > 4.0 ng/mL at approximately 30%. Prostate-specific antigen levels between 4.0 and 10.0 ng/mL have a positive predictive value of 25%; the value increases to 42% through 64% for PSA levels greater than 10 ng/mL. Experts are currently debating if lowering the PSA cutoff may improve survival benefit. However, it is feared that lowering the PSA cutoff would improve sensitivity but decrease specificity, and the number of false-positive cases would increase (Hoffman, 2010).

There are some factors that can increase PSA levels, such as perineal trauma, bicycle riding, or prostatitis. Ejaculation can increase PSA levels by up to 0.8 ng/mL, but the levels will generally return to normal after 48 hours. In general, these transient rises should be rechecked after the altering activity has been discontinued. Medical procedures such as a prostate biopsy can increase PSA levels by as much as 7.9 ng/mL, and they may remain elevated for 2 to 4 weeks following the procedure. Therefore, screening tests should not be performed for at least 6 weeks following any invasive procedure on the prostate (Hoffman, 2010).

Prostate-specific antigen can be evaluated in a variety of ways. Velocity, the change in PSA over a specific amount of time, is also known as PSA slope. A sharp rise from one test to the next may indicate a very aggressive cancer (NCI, 2009). Velocity is given significant practice consideration when screening, considering the aggressiveness of the cancer, as well as determining the risk of recurrence. To correctly interpret velocity it is recommended that at least three PSA values over a time period of at least 18 months be evaluated (AUA, 2009).

Adjusted PSA can also be a consideration. Age-adjusted PSA is used for every decade of life following age 50 to better predict benign vs. malignant disease. There continues to be controversy on the accuracy of age-adjusted PSA. Race-adjusted PSA is also being assessed in optimizing PSA use. The American Urological Association has guidelines regarding age- and race-adjusted levels (AUA, 2009).

Prostate-specific antigen density is the level of PSA in relation to the size of the prostate. Utilizing PSA density alone may lead to overlooking cancer in the patient with an enlarged prostate and also requires the use of transrectal ultrasound (TRUS) or magnetic resonance imaging (MRI) to assess prostate volume. Adjusting the normal value of PSA in relation to the size of the prostate may improve specificity and reduce the number of biopsies performed (AUA, 2009).

Protein patterns have been assessed to determine if more aggressive cancers can be distinguished from less aggressive cancers. The percentage of free PSA has been helpful in determining if a patient has a benign prostate condition vs. cancer. Generally, the free PSA is higher in benign prostatic hypertrophy and the attached (also known as complexed) PSA is higher in prostate cancer. Experts have proposed that only men with low ratios go on to have prostate biopsies (AUA, 2009).

Use of PSA for Screening: Clinical Studies

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is currently accruing data. This study began in 1991 and includes males from Belgium, Finland, France, Italy, Netherlands, Spain, Sweden, and Switzerland, ranging from 50 to 75 years old. The screening group includes 83,645 men and the control group includes 99,393. The screening group receives DRE, PSA, and/or TRUS biopsy and the control group receives no offered screening. The study is collecting data on the outcomes associated with prostate cancer mortality, detection rates, stage of cancer, and quality of life, but the primary endpoint is the rate of death from prostate cancer (Ilic et al., 2008). The preliminary results of the study indicate that there is a reduction in prostate cancer mortality due to PSA screening; however, the rate of overdiagnosis of prostate cancer is estimated to be as high as 50%. Overdiagnosis is defined as no clinical symptoms associated with prostate cancer during a man's lifetime. Therefore, treatment would not have changed outcome in mortality (Schroder, 2009).

The Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial is currently accruing data. This study began in 1993 and includes males ranging from 55 to 74 years old from 10 screening centers in the United States. There are 37,000 participants for both the screening and control groups. The males in the screening group receive DRE, PSA, and lung and colorectal cancer screening. The control group does not have any offered screening. The outcomes being assessed in

relation to prostate cancer include mortality, cancer detection rates, and the stage of cancer at detection (Ilic et al., 2008). Prostate cancer mortality is the primary endpoint (Andriole et al., 2009).

Preliminary data suggest that there was a 22% increase in diagnosis of prostate cancer related to routine screening. The first report published from the PLCO screening trial, which is approximately 67% complete, concludes that after 10 years of follow-up the rate of death from prostate cancer remained low and was not significantly different between the screened and nonscreened groups. The number of men that died from causes not associated with prostate cancer was higher in the screened group. The researchers are unable to determine if the men died because of complications associated with cancer treatment because of overdiagnosis or from comorbidities (Andriole et al., 2009).

Emerging Biomarkers

There continues to be interest in pursuing more accurate prostate cancer predictors because PSA use, along with histologic grade and tumor stage, continue to lack sufficient ability to determine who should or should not receive treatment for prostate cancer. Two biological markers currently under investigation include the *TMPRSS2-ERG* fusion gene as well as prostate cancer gene 3 (*PCA3*). The use of microRNAs (miRNAs) is also being investigated more closely. miRNAs are small, noncoding RNA molecules that regulate messenger RNA (mRNA) to protein. miRNA patterns in normal cells are different than in abnormal cells and may help differentiate cancer by showing a loss of enhancement properties. miRNA can be found in peripheral blood cells and is currently being studied in multiple malignancies (Hunter et al., 2008).

TMPRSS2 is highly prostate-specific and is found fused with the transcription factor gene *ERG* in a high proportion of prostate cancers. The transcription factor *ERG* has been identified in several oncogenic pathways. *TMPRSS2-ERG* is a biomarker that is also showing increased accuracy for predicting if a man's prostate has cancer present. There are different ways to test for the presence of *TMPRSS2-ERG*, such as massaging the prostate gland in order to obtain fluid (NCCN, 2010), performing fluorescence in situ hybridization on circulating tumor cells in peripheral blood (Mao et al., 2008), as well as taking samples from the tumor after prostatectomy (Nam, Sugar, & Wang, 2007). When protein is detected in the circulating blood, there is increased concern regarding the cancer's ability to metastasize (Mao et al., 2008). A study done by Nam et al. (2007) showed a significant association with the *TMPRSS2-ERG* fusion gene and disease relapse among patients diagnosed with clinically localized prostate cancer. The study investigators believe that if the findings are confirmed, this could help identify patients that should be treated aggressively due to an increased risk of disease progression (Nam et al., 2007). Currently, there are no recommended changes in the standard of care for screening those at risk for prostate cancer or for posttreatment assessments based on the results of the studies published on *TMPRSS2-ERG*.

Like *TMPRSS2-ERG*, the use of *PCA3* for prostate cancer detection has shown promising results. Busselmakers et al. (1999) first described the *PCA3* gene by looking at prostate-specific mRNA. Observers noted that prostate-specific mRNA is overexpressed in prostate cancer tissue when compared with benign prostatic tissue.

Galasso et al. (2010) looked at a total of 925 *PCA3* tests. A total of 443 patients had a *PCA3* score of ≥ 35. Of those 443 patients, 105 underwent biopsy or repeat biopsy. In 27 of these patients biopsied, no tumor was noted. Of the remaining patients biopsied, 37 were noted to have high-grade prostate intraepithelial neoplasm and 41 patients were noted to have prostate cancer. Based on the results of this study and other conducted trials, *PCA3* can be a valid tool for guiding practitioners in diagnosing prostate cancer and identifying those patients who would benefit from prostate biopsy.

PCA3 is measured by collecting the first clean catch urine sample following a digital rectal exam, which is required in order to release prostate cells into the urine. *PCA3*, PSA, and mRNA are then quantified by a transcription-mediated amplification technology. Gen-Probe of San Diego developed the Progensa *PCA3* test. In September 2010 Gen-Probe submitted premarketing approval to the US Food and Drug Administration (Kirby, Fitzpatrick, & Irani, 2009).

Not only is this assay seen as a valid tool for prostate cancer detection, but *PCA3* can help guide practitioners in making better decisions re-

garding those patients who need biopsy vs. those whom simply need active surveillance. Because elevated PSA levels can be detected in men with benign prostatic hyperplasia and prostatitis, its specificity for detecting prostate cancer can be low. *PCA3* is specific for prostate cancer and not affected by noncancerous related prostate conditions or prostate volume. Using *PCA3* in addition to other biomarkers, such as the *TMPRSS2-ERG* fusion gene, will provide for more accurate prostate cancer diagnosis and decrease the need for some unnecessary biopsies.

Posttreatment Monitoring Utilizing PSA

Prostate-specific antigen is not only used for prostate cancer screening. The American Urological Association has guidelines associated with the use of PSA in pretreatment staging and posttreatment management of prostate cancer. Serum PSA levels may help identify the risk of extraprostatic extension, seminal vesicle invasion, lymph node involvement, as well as distant metastasis. Patients with PSA levels below 10 ng/mL are most likely to respond to local therapy when determining outcomes based on pretreatment results (AUA, 2009).

The use of PSA for posttreatment evaluation is important in identifying recurrence after definitive therapy. However, there are differences in the interpretation of PSA based on the particular treatment that the patient received. Patients that receive androgen suppression therapy alone should have a decreasing PSA and then a PSA nadir. The length of the PSA nadir following androgen suppression therapy correlates with prognosis of disease. Patients that fail to achieve a PSA nadir of less than 4 ng/mL 7 months after the initiation of therapy have a very poor prognosis. However, the patients that are able to achieve a PSA nadir of less than 0.2 ng/mL have a good prognosis. If a patient received a prostatectomy, PSA is expected to decline consistently and then remain undetectable. Serum PSA should fall to a low level following radiation therapy but may not reach undetectable levels. Prostate-specific antigen values less than 0.2 ng/mL are uncommon following external beam radiation therapy (AUA, 2009).

Posttreatment assessment and management using PSA is frequently seen in the oncology setting. The National Comprehensive Cancer Network (NCCN) guidelines currently recommend PSA and DRE at regular intervals: usually every 6 to 12 months for initial-definitive therapy and every 3 to 6 months for regional or metastatic disease (NCCN, 2010). See Figure 1 for the current posttreatment assessment and management guidelines from the American Urological Association.

Controversies With PSA Use

During the 20-year period since significant PSA testing began there has been a decline in the prostate cancer mortality rate. The ERSPC, one of the largest prostate cancer screening trials, revealed a 20% reduction in prostate cancer mortality with screening. The ERSPC and other screening trials have observed a decline in the incidence of late-stage disease and a rise in the diagnosis of early-stage disease, but overall, screening had little to no effect on the death rate associated with prostate cancer. Studies like the ERSPC have also documented the overtreatment of men with early-stage disease. Much controversy continues to exist as men continue to look to their health-care providers for direction regarding prostate cancer screening (Schröder et al., 2009).

At this time we are unable to predict which men will die *of* prostate cancer and which men will die *with* prostate cancer. An abnormal DRE and/or elevated PSA can lead to more invasive testing before a diagnosis is made. Richard Albin, developer of the PSA screening tool, stated, "PSA screening should absolutely not be deployed to screen the entire population over 50 years of age" (Chustecka, 2010). Albin describes PSA screening as a tool to be used for those who have already been diagnosed with prostate cancer, to evaluate response to treatment, or as a means of surveillance where a rapid rise in number may predict a return of the disease. But to date no one has manufactured a test that differentiates the aggressive, rapid-growing prostate cancer that could potentially be fatal from the slow-growing type that will not lead to a shortened life expectancy.

These are the arguments that have led to the much-publicized controversy currently in the media. In addition to the lack of differentiation associated with PSA, it is expected that mass prostate cancer screening may cost $18 billion for the first year, with much of this money coming from Medicare and the Veterans Administration. The controversy has led to published recommendations by all the ma-

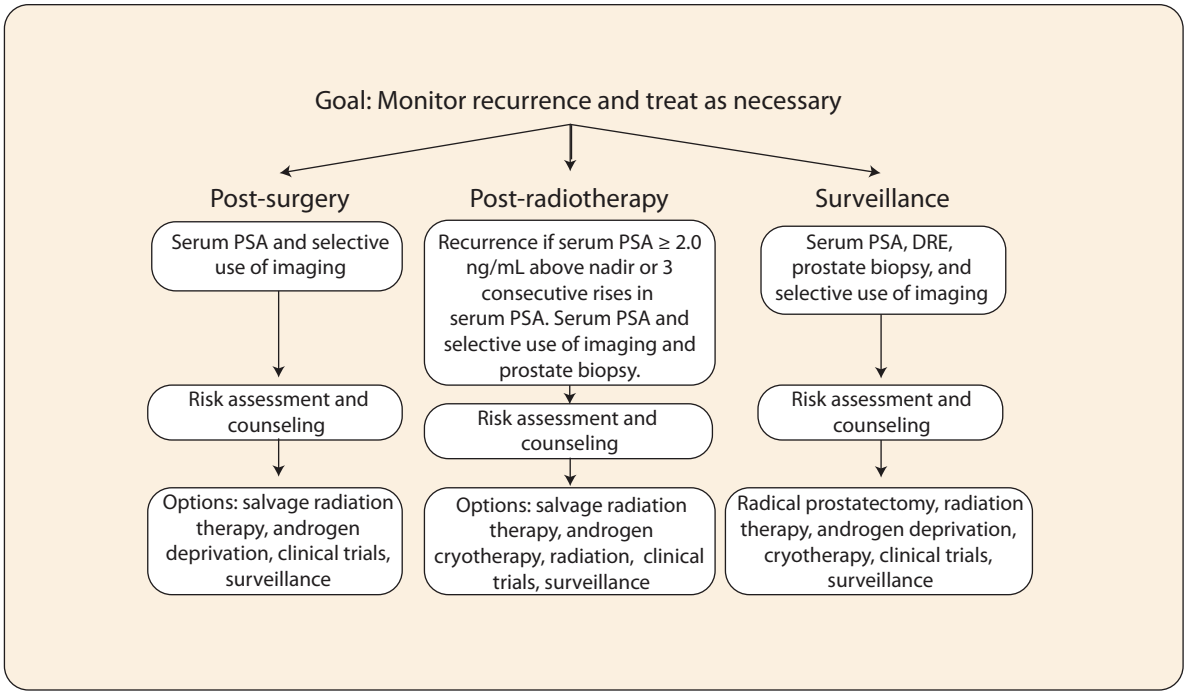

Figure 1. Posttreatment assessment and management. DRE = digital rectal examination; PSA = prostate-specific antigen. Reprinted, with permission, from P. Carroll, P. C. Albertsen, K. Greene, R. J. Babaian, H. B. Carter, P. H. Gann,...A. Zietman, 2009, Prostate-Specific Antigen Best Practice Statement: 2009 Update. American Urological Association Education and Research, Inc., ©2009. Retrieved from http://www.auanet.org/content/media/psa09.pdf

jor supporting organizations, including the American Cancer Society, Centers for Disease Control, US Preventive Service Task Force, American College of Preventive Medicine, and American Urologic Association. These vastly different recommendations have led to much confusion and questions from men electing to be screened and their health-care providers alike (Chustecka, 2010). See Table 1 for a summary of these recommendations.

Role of the Advanced Practitioner

Counseling and identifying patients at risk for developing prostate cancer are the primary roles of advanced practitioners (APs). Counseling for patients is imperative as they are faced with the decision to be tested or not. If tested, what does the result mean for the patient as they look into the future? Advanced practitioners are essential components of the education process. Their role should focus on providing informed and shared decision-making as well as identifying those men that are at high risk for prostate cancer.

As APs counsel patients regarding prostate cancer screening, it is important to encourage the patient to make an informed decision based on his values and preferences. Various support organizations (American Cancer Society, Centers for Disease Control, and Foundation for Informed Medical Decision Making) provide documents that can be downloaded to assist with patient education and decision-making. In addition to sending patients home with these documents, directed discussion regarding PSA screening should occur between the AP and the patient. See Table 2 for a list of key topics that should be addressed in any screening discussion.

Patient selection is an important consideration when reviewing patients to be screened. Most guidelines do not recommend PSA screening for men who have limited life expectancies. The American Cancer Society and the American Urological Association recommend annual PSA for men 50 years and older if they have a 10-year life expectancy. This is defined as having a greater than 50% probability of surviving 10 years (Walter, Bertenthal, Lindquist, & Konety, 2006). When reviewing patients to be screened, patients with moderate to severe chronic obstructive pulmonary disease, end-stage renal disease, end-

Table 1. Current Recommendations for Prostate Cancer Screening

Source	Recommendations
American Cancer Society	Asymptomatic men age 50 and older should be given information regarding screening and should consult with their primary care providers about the risks and benefits of screening in order to make an informed decision. High-risk men should receive the information earlier, between age 40 and 45. Prostate cancer screening should not occur without an informed decision-making process. Asymptomatic men with less than a 10-year life expectancy should not be offered prostate screening.
American Urological Association	Baseline PSA at age 40 if life expectancy greater than 10 years. Annual testing is not considered evidence-based.
US Preventive Services Task Force	Insufficient evidence to recommend routine screening of men less than 75 years of age and recommends against screening any man 75 years and older.
Centers for Disease Control	Follows USPSTF recommendations.
American College of Preventive Medicine	Recommends against routine population screening with DRE and PSA. Men age 50 and older should be given information regarding screening and should consult with their primary care provider about the risks and benefits of screening in order to make an informed decision.

Note. DRE = digital rectal examination; PSA = prostate-specific antigen. Information from ACS (2010), AUA (2009), USPSTF (2010), Schmitz/CDC (2010), and Ferrini/ACPM (2010).

stage congestive heart failure, moderate to severe dementia, and life-limiting cancer may be considered to have limited life expectancies and hence do not need to be screened regardless of their chronologic age.

As APs are discussing PSA screening with their patients, it is essential to assess the patient's level of participation in the screening decision. Many patients want to be informed and are seeking information not from only the AP but from the Internet and friends as well. Other patients are looking for the AP to make the decision for them, and become confused when given options. Advanced practitioners need to meet these patients at their level and work with them to achieve a comfortable choice.

Conclusions

Prostate cancer is the most common cancer in men in the United States, yet the controversy surrounding the appropriate use of screening tools continues to be very prevalent. The intention of screening for any type of cancer or disease is to decrease mortality as well as improve quality of life while limiting the risks associated with the screening and treatment procedures. The DRE is not an adequate screening tool alone because of the limited ability to palpate the entire prostate gland. Prostate-specific antigen testing is helpful, yet great controversy surrounds the actual recommendations for its clinical use. The cost of mass testing as well as the uncertainty of the benefits of screening lead to confusion for patients and healthcare providers. There are many unanswered questions associated with population-based screening, including the rate of overdiagnosis, overtreatment, and quality-of-life improvement. Therefore, ongoing research is necessary to help determine the appropriate population to screen. In addition to ongoing research, further education of patients and their families is essential.

Posttreatment assessment and management for prostate cancer patients undergoing treatment or completing treatment is a bit less controversial. Guidelines on the frequency of PSA testing are not standardized, much like the use of PSA for screening. As we strive for evidence-based practice to guide the provision of care, we

Table 2. Key Points to Be Addressed During a Discussion Regarding PSA Screening

Men should consider prostate cancer an important health concern.
Earlier detection of prostate cancer can occur with screening PSA with or without DRE.
Experts agree that screening for prostate cancer can reduce the risk of dying, but the degree of benefit is unknown.
At the time prostate cancer is diagnosed, it is difficult to predict who may benefit from treatment.
Prostate cancer treatment can cause urinary, bowel, or sexual dysfunction. Side effects are often temporary but for some patients side effects can be severe and permanent.
False-negative and false-positive results can occur with PSA and DRE testing.
Prostate biopsies that occur as a result of an abnormal PSA or DRE can be uncomfortable, cause bleeding, and rarely infection.
Not all men diagnosed with prostate cancer require immediate treatment.

Note. DRE = digital rectal examination; PSA = prostate-specific antigen. Based on information from Mulcahy (2010) and the American Cancer Society (2010).

must continue to raise issues of debate until there is either a more sensitive test for prostate cancer or more standardized guidelines supported by ongoing research. As we wait for additional research, which may or may not make screening less controversial and more standardized, APs are at the front lines educating patients and guiding them through making informed decisions about prostate cancer screening. The time taken to provide the extra education and allow for dialog is time well spent as patients continue to be faced with these difficult decisions.

DISCLOSURES

The authors have no potential conflics of interest to disclose.

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