

Pitfalls of State-of-the-Art Prostate Cancer Screening

A White Paper for Primary Care Clinicians

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Prostate cancer is the most common nonskin cancer diagnosed in men, with an estimated 220,800 new cases diagnosed in 2015, and accounting for an estimated 27,560 deaths in 2015.¹ Approximately 1 in 7 men will be diagnosed with prostate cancer during his lifetime.² It is the second leading cause of cancer deaths in men after lung cancer,¹ and is a heterogeneous disease in severity, ranging from slow-growing indolent tumors to rapidly progressing, highly aggressive carcinomas associated with significant morbidity and mortality.³

Typically, prostate cancer develops slowly, with a long preclinical phase such that most men with prostate cancer die of other causes before their disease becomes symptomatic.⁴ The probability of survival in the next 5 years is near 100% for patients with localized or regional disease, and increases with incremental prior years of survival (Figure 1).⁵ The lifetime risk of dying of prostate cancer is less than 3%,⁶ with about 2% of all prostate cancer deaths occurring before age 55 years, 29% occurring between age 55 and 74 years, and 69% at age 75 years and older (Figure 2).⁵

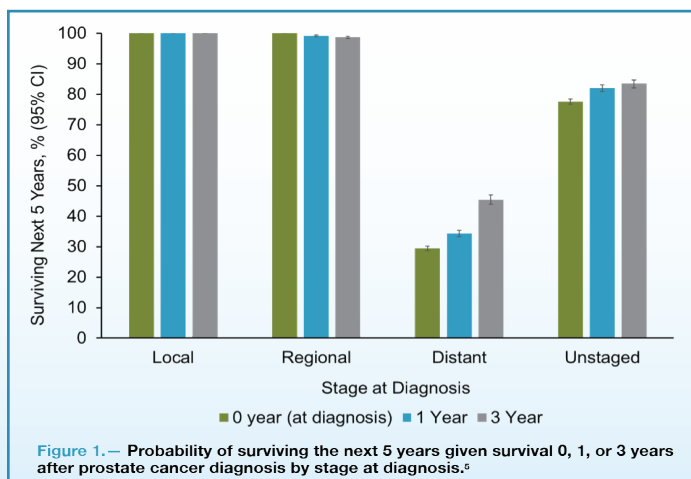


Figure 1.— Probability of surviving the next 5 years given survival 0, 1, or 3 years after prostate cancer diagnosis by stage at diagnosis.⁶

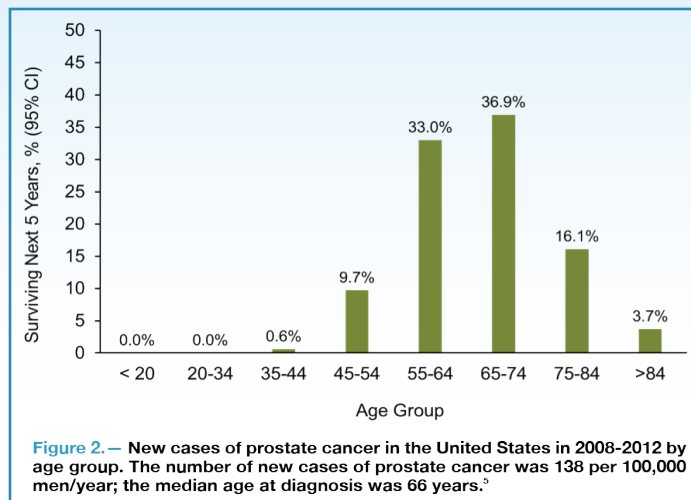


Figure 2.— New cases of prostate cancer in the United States in 2008-2012 by age group. The number of new cases of prostate cancer was 138 per 100,000 men/year; the median age at diagnosis was 66 years.⁵

Prostate Cancer Screening — Controversy and Shortcomings

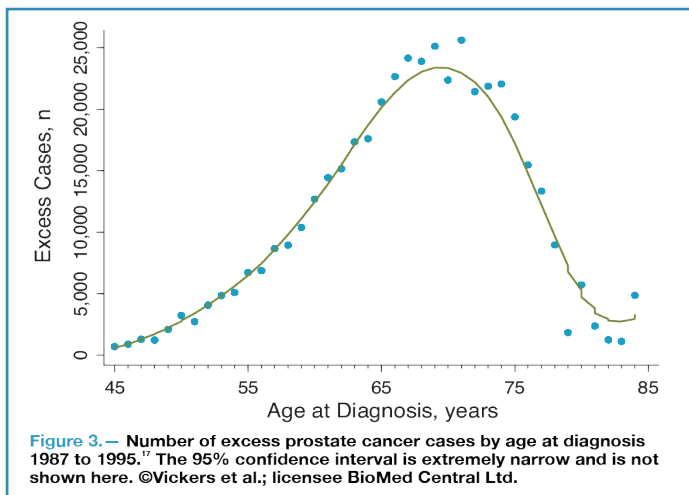
Preventive services, such as prostate cancer screening, fall largely on the shoulders of primary care clinicians.⁷ In the United States, early detection of prostate cancer is driven by prostate-specific antigen (PSA)-based screening, followed by prostate biopsy for diagnostic confirmation.⁸ Approximately 19 million men undergo PSA screening annually, resulting in approximately 4.7 million abnormal findings on tests (based on a PSA > 4.0 ng/mL) leading to approximately 1.3 million biopsy procedures performed.⁹

Deaths in the United States from prostate cancer have decreased approximately 4% per year since 1992 (5 years after the introduction of PSA testing)¹⁰; however, there are conflicting data that fail to convincingly demonstrate a significant decrease in prostate cancer-specific mortality attributable directly to PSA screening.¹¹⁻¹⁴

The vast majority of men with prostate cancer have clinically localized disease at a potentially more curable stage, which is attributable to widespread use of PSA screening.^{3,15} However, the risks

associated with prostate cancer screening with PSA are considerable, and must be weighed against the potential advantage of the still-debated reduction in cancer-specific mortality.¹⁶ Risks include a high rate of false-positive results, complications associated with prostate biopsy, and the serious consequences of prostate cancer treatment.¹⁶

The widespread use of PSA screening has led to an increase in the rate of negative results on biopsies (ie, false-positive PSA test results), as well as a high rate of overdiagnosis or overdiagnosis of prostate cancer (Figure 3).¹⁷



PSA screening has resulted in substantial overtreatment (with attendant adverse effects) of potentially indolent tumors that would have remained asymptomatic and not required treatment for the remainder of a man's life had tumors not been detected via PSA screening and subsequent biopsy.^{3,15} Overdiagnosis is generally defined in this context as detection of a prostate cancer that would have remained asymptomatic and undetected during an individual's lifetime in the absence of screening.^{3,8} Estimates from the 2 largest prostate cancer screening trials suggest overdiagnosis rates, based on PSA screening, of 17% to 50%.³ The rate of overdiagnosis and subsequent overtreatment

secondary to PSA-based prostate cancer screening appears to be greater than that for other cancers for which routine screening currently occurs (eg, breast, colorectal, or cervical cancers).¹⁸ According to a national registry of men diagnosed with prostate cancer in community-based urology practices in the United States, surgery rates for low-, intermediate-, and high-risk cancer were approximately 50%, 70%, and 50%, respectively between 2010 and 2013.¹⁹ Rate of radiation therapy among those same groups was approximately 10%, 20%, and 20%, respectively, and androgen deprivation therapy use was approximately 0%, 5%, and 25%, respectively.¹⁹

Positive PSA test results of 3 to 10 ng/mL have an approximate 70% chance of being false positive.¹⁶ Even after multiple screening tests, there is still a 12% to 13% risk of a false-positive test result.¹⁶ The common PSA threshold for biopsy of greater than 4.0 ng/mL is associated with a positive predictive value of about 30% in men aged 50 years or older, and a negative predictive value of about 85% in men with a median age of 69 years at biopsy.²⁰ At 9 years of follow-up from the large European Randomized Study of Screening for Prostate Cancer (ERSPC) in 182,000 men, 75.9% of men who underwent biopsy after elevated results on PSA (cutoff varied by country between 3.0 and 4.0 ng/mL) had a false-positive result.¹⁸

PSA-driven false-positive results, overdiagnosis, and overtreatment of prostate cancer are associated with a number of potentially harmful sequelae that appear to greatly outweigh the modest, at best, benefits of PSA screening (Table).²¹ Based on an interpretation of the 2 major trials of PSA screening (the US Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial and the ERSPC), the US Preventive Services Task Force (USPSTF)

Harmful Outcomes Associated With PSA Screening and Subsequent Overdiagnosis and Treatment

Harmful Outcome	Approximate Risk	References
<i>Harms of Screening</i>		
Patient anxiety about developing prostate cancer, for up to 1 year after screening (men with negative prostate biopsy after suspicious PSA screening test)	26%	Fowler et al, 2006 ²³
Additional PSA test, biopsy, and/or urologist visit over the next year (vs patients with initial negative PSA result [< 2.5 ng/mL])	73% vs 42%; 15% vs 1%; 71% vs 13%, respectively	Fowler et al, 2006 ²³
Lead time*	5.4 to 6.9 years	Draisma et al, 2009 ⁴²
<i>Harms of Biopsy</i>		
Moderate or major bothersome symptoms, including pain; fever; blood in urine, semen, or stool; infection; and temporary urinary difficulties	Up to 32%	Rosario et al, 2012 ²⁶
Hospitalization	1% to 6.9%	Moyer et al, 2012 ³ Loeb et al, 2011 ²⁵
<i>Complications of Treatment</i>		
Serious CV event due to treatment	2 in 1000 men	Moyer et al, 2012 ³
DVT or PE due to treatment	1 in 1000 men	Moyer et al, 2012 ³
Erectile dysfunction due to treatment	29 in 1000 men; up to 19% to 27%	Moyer et al, 2012 ³ Wolf et al, 2010 ²²
Urinary incontinence due to treatment	18 in 1000 men; up to 12% to 16% long term	Moyer et al, 2012 ³ Wolf et al, 2010 ²²
Death due to treatment	< 1 in 1000 men; 0.1% to 0.2% within 30 days	Moyer et al, 2012 ³ Wolf et al, 2010 ²²

CV, cardiovascular; DVT, deep vein thrombosis; PE, pulmonary embolism.

*Average time by which screening advances diagnosis of prostate cancer among patients who would have been diagnosed with prostate cancer during their lifetimes in the absence of screening.

determined that the benefit of PSA screening and early treatment ranges from 0 to 1 cancer deaths avoided per 1000 men screened.³

The most frequently reported direct harms associated with prostate cancer screening relate to anxiety.²² Two well-designed surveys indicate that men with false-positive PSA results have greater short-term and long-term prostate cancer anxiety than do men with true-negative results (26% vs 6% after 1 year [$P < .001$] in 1 study), and that men with

false-positive results have more subsequent tests/visits compared with men who have true-negative results.^{23,24} This is 1 of several reasons why most clinical practice guidelines regarding PSA screening now encourage shared decision making between clinician and patient, with the patient being informed of the potential benefits and harms of screening.^{7,20} Such guidance, however, places primary care clinicians in a somewhat untenable position, given the lack of additional options to help guide primary care clinicians in determining when referral to a urologist for further evaluation is warranted.

Men who are referred for biopsy based on PSA

test results face prostate biopsy-related risks such as bleeding, infection, and hospitalization due to complications.^{22,25} Estimated incidence of hematuria is approximately 6% to 13%, but the risk of serious bleeding requiring transfusion is low. The estimated rate of urinary tract infection is 0.3% to 4%, and that of serious infection is $< 2\%$.²² There is a 2.65-fold increased risk (95% confidence interval [CI], 2.47-2.84; $P < .0001$) of hospitalization within 30-days of the procedure owing to infectious or noninfectious complications compared with a control population,

based on analysis of a Medicare database (6.9% vs 2.7%).²⁵ Interim results of an ongoing, randomized trial reported that 32% of men experienced 1 or more moderate/major adverse events after prostate biopsy that required clinician follow-up, including pain; fever; blood in urine, semen, or stool; infection; transient urinary difficulties; or other issues.²⁶

Patients who are treated for potentially asymptomatic prostate cancer are at risk for the adverse events associated with such treatment. Radical prostatectomy is associated with a 20% increased absolute risk for urinary incontinence and a 30% increased absolute risk for erectile dysfunction compared with watchful waiting after 1 to 10 years; perioperative deaths or cardiovascular events occur in approximately 0.5% or 0.6% to 3% of patients, respectively.³ Radiation therapy is associated with a 17% absolute increased risk for erectile dysfunction and an increased risk for bowel dysfunction compared with watchful waiting after 1 to 10 years.³

Attendant with the increased overdiagnosis and overtreatment associated with PSA screening are the associated costs. Approximately \$1.86 billion is spent annually on PSA tests alone,⁹ and the estimated national expenditure for care of men with prostate cancer in 2014 in the United States was \$13.4 billion, according to the National Cancer Institute.²⁷

Recent healthcare legislation (ie, the Affordable Healthcare Act of 2011) emphasizes an increased reliance on primary care providers to coordinate patient's care and reduce reliance on specialty care, thus increasing the depth and breadth of diagnostic and treatment services expected at the primary care level.²⁸ The resulting shift toward accountable care organizations (ACOs) and patient-centered

medical home models has put increased pressure on primary care providers to be accountable for healthcare spending as well as healthcare quality.²⁹ In this context of expectation for more in-depth diagnosis and treatment at the primary care level, and increased pressure to control healthcare costs, the shortcomings of PSA-based screening, and costs associated with subsequent overdiagnosis and treatment highlight the need for better diagnostic tools to allow the primary care clinician to more effectively triage only those patients likely to benefit from more costly urology specialty care.

Prostate Cancer Screening – Guidelines

In 2012, the USPSTF published guidelines recommending against PSA-based screening for prostate cancer in the general population, citing convincing evidence that PSA-based screening results in overdiagnosis of asymptomatic cancer that would likely have remained asymptomatic for the man's lifetime, resulting in increased biopsies and treatment with little to no demonstrated reduction in prostate cancer mortality.³

Clinical practice guidelines of major medical societies regarding screening with PSA conflict with those of the USPSTF, with most recommending shared decision-making between clinician and patient, consideration of risk factors, and recommendations regarding screening intervals.²⁰ For example, the American College of Physicians (ACP) recommends screening with shared decision making for men aged 50 to 69 years with a life expectancy of greater than 10 to 15 years.³⁰ ACP also recommends screening at 45 years of age for men at higher risk for prostate cancer (patients who are black, and those patients who have a first-degree relative who was diagnosed with prostate cancer before 65 years of age), and at 40

years of age for men with multiple family members diagnosed with prostate cancer before 65 years of age.³⁰ Intervals longer than 1 year between screening PSAs are recommended.³⁰ The ACP guidelines are largely similar to those promulgated by the American Urological Association (AUA) and the American Cancer Society (ACS).^{8,22} ACS guidelines further recommend a PSA level of ≥ 4.0 ng/mL as the cutoff for referral to a urologist for further evaluation or biopsy for men at average risk for prostate cancer, and a PSA level of 2.5 ng/mL to 4.0 ng/mL as the range in which to consider an individualized risk assessment incorporating other risk factors that may be used to recommend a biopsy.²²

Despite conflicting guidelines, and the shortcomings and risks associated with PSA screening, it continues to be used as a primary screening tool by many primary care clinicians, and is then repeated by a urologist on patient referral because of the elevated PSA levels identified by the primary care clinician at the outset. Continued use of PSA screening may be due to a clinician's fear of missing a serious, potentially lethal cancer or for potential liability concerns, or screening may be performed at a patient's request.³¹⁻³⁴

New Developments in Screening and Diagnosis of Prostate Cancer

The focus of early detection has shifted from efforts to diagnose any and all prostate cancers to an effort to diagnose clinically significant prostate cancers at an early stage.³⁵ This is reflected in a trend toward a decreased number of initial biopsy procedures performed (from 24% to 16%), increased use of repeat PSA testing (from 72% to 82%), and increased use of prostate cancer antigen-3 (PCA3) testing (from 11% to 27%) by urologists for those

patients referred to their offices from primary care practices because of previous elevated PSA screening results.³² Furthermore, several recent studies report decreased frequency in PSA screening among primary care clinicians subsequent to the May 2012 USPSTF recommendation,^{32,36,37} possibly reflecting an increased selectivity in screening practices on the part of clinicians based on patients' age, prior PSA level (if previously screened), or other risk factors for prostate cancer.

Few additional options are currently available to guide primary care clinicians in determining when referral to a urologist for further evaluation is warranted, or to guide urologists in determining whether a first or follow-up biopsy is warranted. Fear of occult prostate cancer leads to additional procedures; therefore, many men receive second, third, and fourth repeat biopsy procedures to rule out the presence of cancer.³⁸ These shortcomings have led many researchers to investigate ways to optimize the use of PSA and develop novel serum and tissue biomarkers to address the need for more accurate, dependable screening tools. The goal is to identify patients more likely to benefit from referral and further evaluation, biopsy, and potentially from treatment for early prostate cancer, while reducing inaccurate readings, unnecessary invasive testing in healthy men, and attendant excess healthcare costs.

Laboratory tests account for only approximately 2.3 cents of every dollar spent on healthcare, but their results affect between 70% and 80% of clinical decisions made.³⁹ Therefore, more accurate diagnostic laboratory tests to screen for prostate cancer are needed to help primary care clinicians more effectively coordinate patient care and triage appropriate patients to specialty care for further workup and treatment.

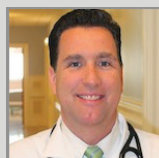
Apifyn[®] is the only cancer specific, nongenomic, non-PSA-based blood test designed to aid clinicians in the assessment of risk for the presence of prostate cancer. Apifyn has been developed using breakthrough technology that involves the use of autoantibodies as biomarkers against peptides derived from prostate cancer tissue.⁴⁰ Apifyn measures 8 signature autoantibodies in the blood stream that are released by the immune system in response to the presence of prostate cancer.⁴¹ The scores from the developed algorithm can be used to indicate a relative high or low risk of the presence of autoantibodies known to be associated with an immune response to prostate cancer, particularly for patients with intermediate (4.0 to 10 ng/mL) PSA levels that are associated with a high rate of false-positive results due to a lack of sensitivity and specificity in this range.⁴¹ Measurement of these cancer-specific biological markers may be used in men with an elevated PSA (> 2.5 ng/mL) to help provide additional insight to support a more informed clinical decision about when to refer to a urologist for further evaluation. Potential benefits of Apifyn to aid in diagnostic decisions may include earlier detection of cancer and, therefore, improved survival rates, as well as a reduction of unnecessary biopsies, with a consequent reduction in associated morbidity and healthcare costs related to overdiagnosis and overtreatment.

Several other serum biomarkers are available to aid primary care clinicians in prostate cancer diagnosis, but most, unlike Apifyn, are based on PSA testing. Prostate Health Index (PHI) is a multi-analyte immunoassay that measures PSA, free PSA, and p2PSA in serum.¹⁵ The 4Kscore[®] Test is also a multi-analyte immunoassay that measures total PSA, free PSA, intact PSA, and human kallikrein-related peptide 2 (hk2) in blood and utilizes an algorithm to calculate the risk for high-grade prostate cancer.¹⁵

Conclusions

The degree of potential overdiagnosis and associated overtreatment of prostate cancer appears to be greater than that for any other cancer for which routine screening currently occurs and is associated with serious adverse effects. PSA-based screening for prostate cancer, including its limitations, has been well understood by clinicians and reimbursement authorities for over 3 decades. There is a need to move beyond PSA testing with new biological markers that are cancer specific to improve early detection of cancer. Such markers will more accurately identify patients who are most likely to benefit from referral to a urologist for further evaluation, biopsy and, potentially, treatment for early prostate cancer while reducing inaccurate readings, unnecessary invasive testing in healthy men, and associated morbidity and healthcare costs.

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