

Prostate Cancer Screening: Navigating the Controversy

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Despite advances in diagnosis, treatment, and patient outcomes, prostate cancer remains an important public health problem. In the United States in 2010, an estimated 217,730 new cases of prostate cancer were diagnosed and 32,050 men died as a result of this disease [1]. Prostate cancer is the second leading cause of cancer death in US men. The natural history of prostate cancer is remarkably heterogeneous, ranging from clinically silent tumors never destined to impact a patient to aggressive, metastatic cancers which cause considerable morbidity and patient death. A recent autopsy study revealed a prostate cancer prevalence of 1 in 3 for men aged 60–69 [2]. However, the risk of death from prostate cancer is only 3.4%, highlighting the variable natural history of prostate cancer.

Estimates of US national health-care expenditures for prostate cancer care are expected to increase dramatically between now and 2020 from \$11.85 billion to \$16.35 billion [3]. Zhang et al. analyzed the growth of prostate cancer spending by analyzing Surveillance, Epidemiology, and End Results (SEER)-Medicare data from 1992 to 2003 and concluded that Medicare

spending for prostate cancer care increased by 20% [4]. Effective strategies of prevention, screening, and treatment are paramount to reduce the burden and cost of this disease. The goal of early detection by screening is to reduce morbidity and mortality of prostate cancer.

PSA-based screening has been controversial since it was first introduced in the late 1980s. Although PSA testing was originally intended to assess tumor recurrence or progression after treatment, it began to be used as a screening test despite the absence of level I evidence after publication of guidelines from the American Cancer Society and the American Urological Association beginning in the early 1992 [5, 6]. The adoption of PSA as a screening test has been associated with stage migration with a reduction in mortality and incidence of metastatic prostate cancer [7, 8]. However, many prostate cancers diagnosed based on PSA-based screening may have remained clinically indolent, never causing any symptoms. This phenomenon has resulted in overdiagnosis and overtreatment of clinically insignificant prostate cancer. Screening-related complications resulting in hospital admission from transrectal ultrasound-guided prostate biopsy have also risen sharply in the past 10 years, primarily due to infection but also due to bleeding and urinary obstruction [9]. The challenge in prostate cancer screening is to develop a sensitive and specific test that differentiates between cancers that would remain clinically indolent and those that would cause morbidity or death to the patient.

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Principles of Screening for Cancer

In 1907, Charles Childe developed the paradigm for cancer screening in a book titled *The Control of a Scourge, Or How Cancer is Curable*. Childe argued for the aggressive pursuit of the subtlest deviations from normal to identify asymptomatic latent cancers for curative treatment, stating that delay in cancer diagnosis is what makes cancer lethal [10]. Although it may seem intuitive that early diagnosis and treatment of an asymptomatic cancer would logically result in a benefit to patients, not all cancers are destined to become symptomatic or result in death, especially low-grade and low-stage cancers. In the 1960s, medicine began to question the linear model of carcinogenesis and the overall utility in widespread cancer screening. The United States Preventive Services Task Force was created in 1984 and has shifted the paradigm by examining the medical evidence for cancer screening. The USPTF has shifted away from the intuitive approach and developed a rigorous analytical framework for developing screening recommendations.

Cancer screening is defined as testing for cancer in a patient when no signs or symptoms exist. The principles of an effective prostate cancer screening test are important to review. An effective screening test must have the following attributes:

- It must capture a larger number of earlier stage prostate cancers
- It must improve prostate-cancer-specific survival
- It must improve overall patient survival
- It must decrease cancer-related morbidity

The introduction of PSA-based screening has certainly led to an increase in the diagnosis of a larger proportion of clinically localized prostate cancer. Mettlin and colleagues demonstrated the effectiveness of PSA-based screening in a study of 2,999 men and concluded that PSA testing resulted in the diagnosis of a more favorable stage distribution [11]. Additionally, Catalona et al. demonstrated that PSA-based serial screening resulted in the diagnosis of less advanced, clinically localized prostate cancer in a study of more

than 10,251 men [12]. This study compared 266 patients who underwent biopsy for an abnormal DRE versus an initial and serially PSA-screened population and concluded that PSA-based serial screening results in the diagnosis of a larger proportion of clinically localized, less advanced prostate cancer compared to those patients with an abnormal DRE alone.

Since the introduction of PSA-based prostate cancer screening in the United States, prostate cancer mortality has steadily declined. An analysis of the Surveillance, Epidemiology, and End Results (SEER) Program database revealed a 37% decrease in prostate-cancer-specific mortality since 1992. However, it is not clear that PSA-based screening is the only reason for the observed marked decline in mortality. Overdiagnosis of insignificant prostate cancers, lead-time bias, and healthy screened bias, as well as advances in the treatment of prostate cancer, may contribute to an improved prostate-cancer-specific mortality. In a provocative study that examined two regional cohorts from Seattle and Connecticut which experienced markedly different PSA-based screening, Lu-Yao et al. concluded that although the rate of PSA testing in Seattle was 5 times higher than Connecticut, the rate of prostate cancer mortality at 11 years of follow-up was virtually the same. Etzioni and colleagues used a surveillance modeling approach to quantify the association between PSA-based screening and the decline in distant stage incidence, as has been observed since the introduction of PSA testing [13]. This study concluded that PSA-based screening is likely accounted for 14% of the observed decline since 1990, accounting for 2/3 of the overall decline. The results from large randomized trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC), and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial have recently been reported and show efficacy to screening. However, screening-related overdiagnosis and attendant overtreatment were common to both trials. The Holy Grail for prostate cancer continues to be measures to differentiate indolent from aggressive cancers.

History of Prostate Cancer Screening

Hugh Hampton Young was the first urologist to advocate screening for prostate cancer in 1905 with the digital rectal examination (DRE). DRE was advocated as a method to identify early changes in the prostate consistent with prostate cancer, suitable for curative radical prostatectomy. Unfortunately, most cancers were found to be advanced at the time of diagnosis.

Prostate cancer screening did not change significantly for the next 80 years. A digital rectal examination is known to be insensitive as a screening tool for the detection of low-grade, low-stage prostate cancer. In 1994, Catalona et al. conducted a large prospective trial involving 6,630 patients

to compare the efficacy of DRE and serum PSA [12]. Quadrant biopsies were performed if the PSA was >4 ng/l or if the DRE was suspicious. This study demonstrated that DRE was less sensitive than PSA for the detection of prostate cancer. Combining DRE and PSA as a screening test for prostate cancer improved the detection of organ-confined disease by 78% over DRE alone.

The introduction of PSA-based prostate cancer screening in 1987 by Stamey et al. resulted in a “harvest effect,” and the observed incidence of prostate cancer rose dramatically, peaking in 1992 (Fig. 2.1)[14]. The abrupt increase in prostate cancer incidence between 1987 and 1992 is attributable largely to the introduction and rapid dissemination of PSA-based prostate cancer screening [15].

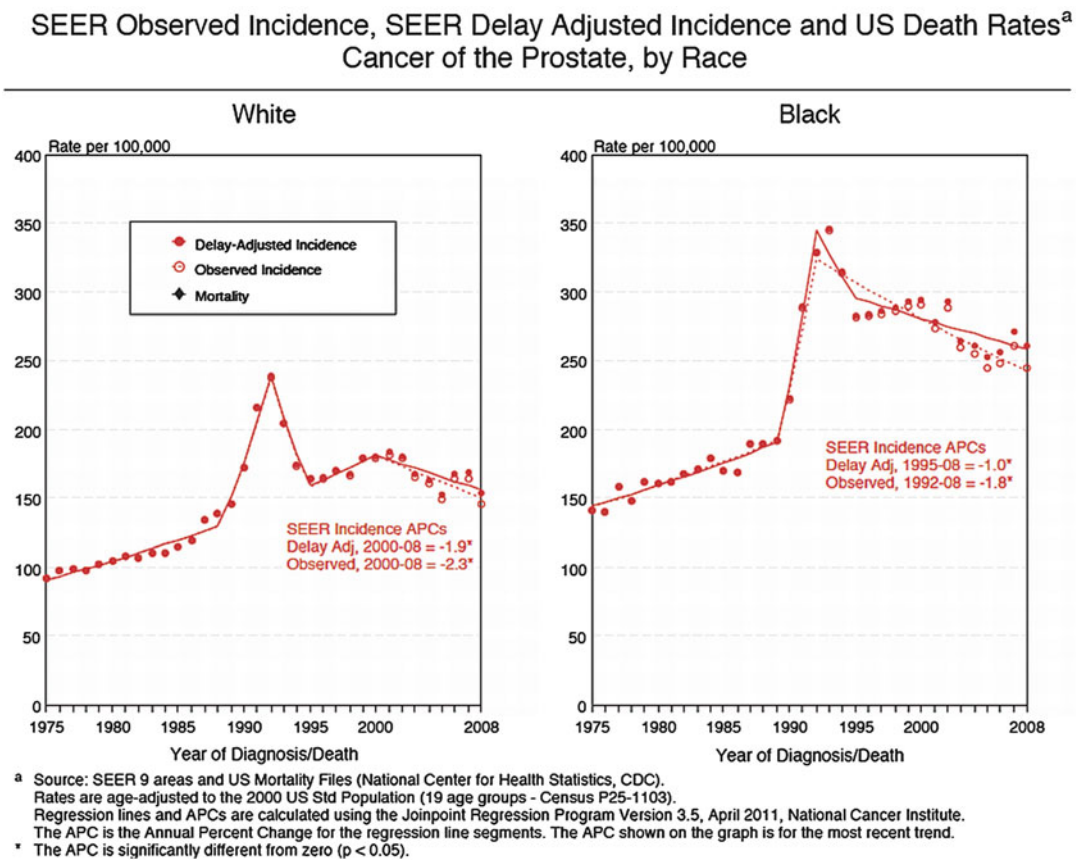


Fig. 2.1 SEER observed incidence, SEER delay-adjusted incidence, and US death rates (Adapted from: http://seer.cancer.gov/csr/1975_2008/sections.html)

PSA-Based Screening for Prostate Cancer

In 1970, Ablin et al. characterized what is now known as PSA. The first application of PSA analysis was to utilize the test in sex crimes due to its high concentration in human semen [16]. PSA is a member of the human kallikrein gene family and is a serine protease produced by prostatic epithelium. Nadji and colleagues demonstrated that PSA is specific to the prostate, and researchers then began to investigate if PSA could be used as a biomarker for prostate cancer [17]. Prior to using PSA for prostate cancer screening, serum prostatic acid phosphatase (PAP) was utilized as a marker for prostate cancer. However, in comparison to PSA, PAP was not found to be a sensitive marker for clinically localized disease and was not used for prostate cancer screening. Seamonds and colleagues compared PSA and PAP and concluded that for clinically localized disease, PSA was more sensitive than PAP [18]. In 1987, Stamey et al. confirmed the improved sensitivity of PSA by evaluating 699 patients, 378 of whom had prostate cancer and concluded that PSA is more sensitive for prostate cancer, but both PSA and PAP are not specific [14]. Beginning in the early 1990s, the first of many large PSA screening studies began to appear in the medical literature [19–22]. In 1991, Catalona et al. ushered in PSA-based prostate cancer screening. In this landmark paper, Catalona and colleagues demonstrated the utility of PSA-based prostate cancer screening by concluding that the combination of serum PSA and digital rectal examination provides an improved method of detecting prostate cancer. This finding led to widespread adoption of PSA-based screening in the United States and an explosion in the number of prostate cancer diagnoses. A 1995 analysis of SEER and Medicare claims data concluded that the exponential increase in prostate cancer detection was due to widespread rapid adoption of PSA-based screening. Importantly, this study raised serious concerns regarding overdiagnosis of a large pool of latent disease, never destined to cause harm to the patient. Furthermore, Potosky and colleagues stated that the implementation of a highly

sensitive test such as PSA was a “double-edged sword” because it uncovered a broader spectrum of disease that may have never been detected and whose natural course and response to radical treatment we know little about [23].

Operating Characteristics of PSA

Central to understanding screening tests is a thorough knowledge of the performance characteristics of the test. A receiver operating curve (ROC) is a plot of the true-positive rate (sensitivity) versus the false-positive rate ($1 - \text{specificity}$). A perfect screening test would, as seen in the upper left of the graph in Fig. 2.2, have 100% sensitivity and 100% specificity. Graphically, an ROC plot demonstrates the trade-off between true-positive and false-positive results. In 2005, Thompson et al. analyzed Prostate Cancer Prevention Trial (PCPT) data and illustrated important operating characteristics of PSA-based prostate cancer screening, as seen in Fig. 2.3 [24]. This study showed that PSA is more sensitive for higher Gleason grade cancers and concluded that lowering the threshold for prostate biopsy would increase the detection of insignificant prostate cancers.

Applying ROC analysis to PSA has been challenging because of verification bias and spectrum bias. Verification bias is introduced in cancer screening when verification of disease status (prostate biopsy) is determined by a positive test (abnormal PSA or DRE). Punglia et al. determined the impact of verification bias by modeling and demonstrated that adjustment for verification bias improved the area under the curve (AUC) from 0.69 to 0.86 for men <60 years old and implied that lowering the PSA threshold for prostate biopsy from 4.1 to 2.6 ng/mL in men <60 years old would double the cancer detection rate from 18% to 36% [25].

Spectrum bias refers to a change in performance of a screening test based on a change in patient population. Ransohoff and colleagues first described spectrum bias in 1978 and stated that “unless an appropriately broad spectrum is chosen for the diseased and non-diseased patients who comprise the study population,”

Fig. 2.2 Receiver operating characteristic curve

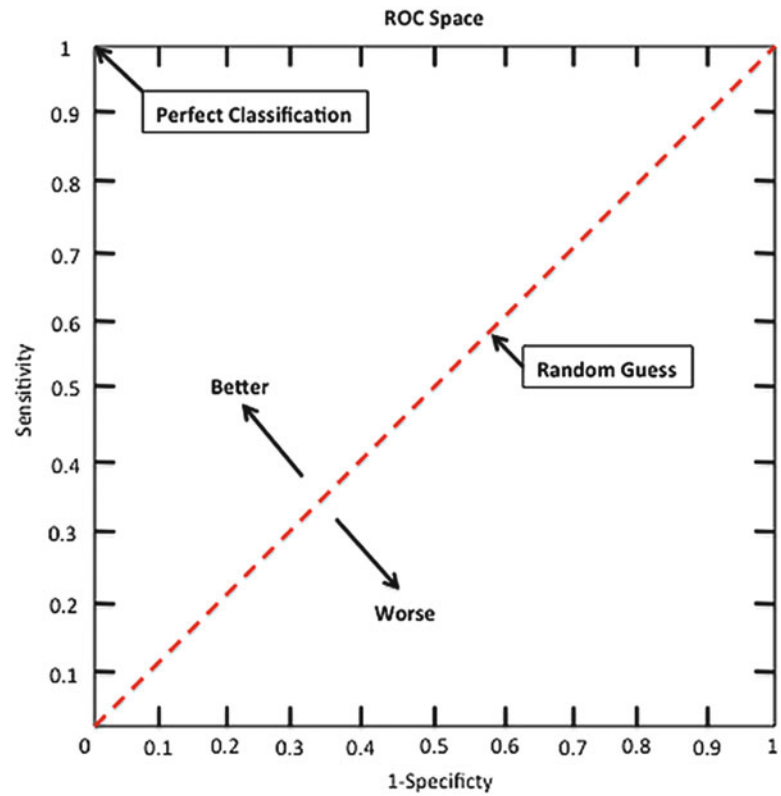
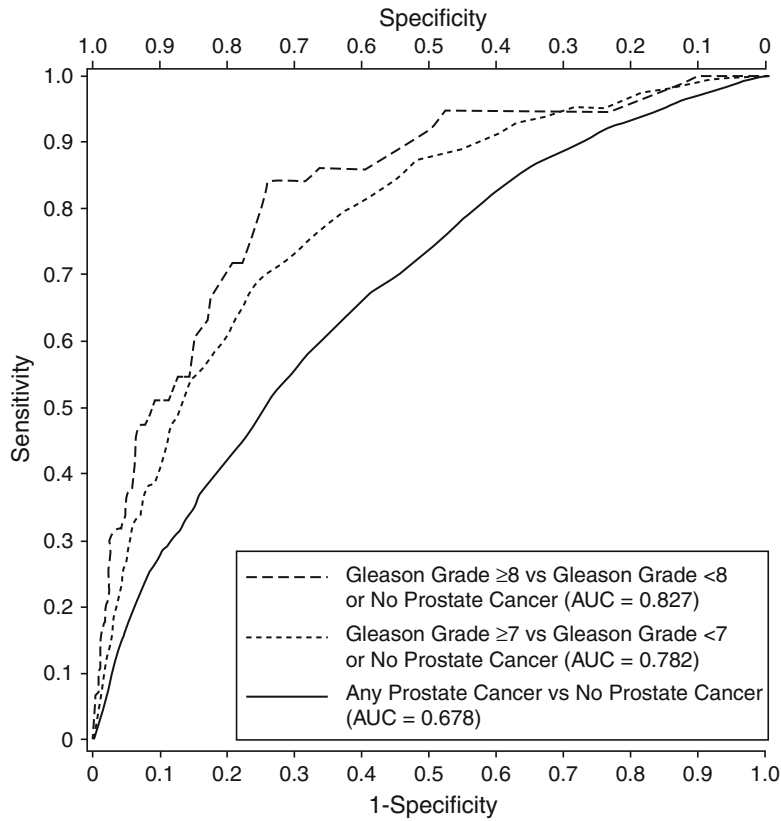


Fig. 2.3 Receiver operating characteristic curve for PSA. As Gleason grade increases, PSA becomes more sensitive and specific for the detection of prostate cancer



diagnostic accuracy of the test may be biased and overestimated if a test is evaluated in a population known to have the disease but applied to a group of normal subjects, as in annual PSA-based prostate cancer screening [26]. A method to reduce spectrum bias in the development of screening tests is to include a broad range of disease severity in the population undergoing the test.

PSA Derivatives

In order to enhance the sensitivity and specificity of PSA-based screening, researchers have investigated multiple PSA derivatives, including age-specific PSA, PSA velocity (PSAV), PSA density (PSAD), %free PSA (fPSA), and PSA isoforms. PSA derivatives attempt to differentiate elevated PSA from benign prostatic hyperplasia.

Age-specific PSA has been used in an attempt to detect potentially fewer clinically insignificant cancers. Serum PSA increases an average of age-specific PSA as men age due to a higher volume of tissue associated with benign prostatic hyperplasia. Annually, serum PSA has been observed to increase in men with and without benign prostatic hyperplasia (BPH). The rate of change in serum PSA for men without BPH has been observed to be 0.04 ng/mL/year, while for those with BPH, the rate of change of PSA was higher at 0.07–0.27 ng/mL/year [27]. Age-specific ranges for normal PSA were proposed by Oesterling in 1996 [28]. Regarding the clinical utility of using age-adjusted PSA, studies have reported conflicting results. Catalona et al. prospectively evaluated 6,630 men to determine the effect of using age-specific PSA ranges on biopsy and cancer detection rates and noted that if biopsy criteria were lowered to 3.5 ng/mL in men aged 50–59, a 45% increase in biopsies would be performed with a calculated 15% increase in prostate cancer detection [29]. On the other hand, if the PSA threshold were increased to 4.5 ng/mL in the 60–69 age group, 15% fewer biopsies would be performed, resulting in a decrease in the cancer detection rate by 8%. Most interestingly, increasing the PSA threshold in men more than 70 years old would result in 44% fewer biopsies and would not detect 47% of organ-confined cancers. This study

concluded that the general guideline for performing a biopsy should remain at 4.0 ng/mL.

In a pathological review of 4,597 men with clinically localized prostate cancer, Partin and colleagues analyzed the effect of using age-adjusted PSA and concluded that age-specific PSA increased the detection of clinically localized, potentially curable prostate cancer in younger men by 18% and decreased the detection rate in older men by 22% but that 95% of these tumors had favorable pathology. These studies point to common problems associated with age-specific PSA, that using different PSA thresholds results in overdetection of prostate cancer in younger men and underdetection of potentially significant tumors in older men.

PSA velocity has been studied to improve screening for prostate cancer. In 1992, one of the first research groups to investigate PSA velocity reported results after studying 16 men with no evidence of prostate cancer, 20 men with BPH, and 18 men with prostate cancer [30]. Their analysis revealed important characteristics of PSA metrics in the years prior to a diagnosis of prostate cancer; noting an association with an increased PSA velocity >0.75 ng/mL/year is a specific marker for prostate cancer. In this study, 72% of men with prostate cancer were noted to have a PSAV >0.75 ng/mL/year for men with a PSA between 4 and 10 ng/mL/year. Additionally, serial PSA measurements over a minimum of 18 months are required to estimate PSAV [31–33].

PSA may be elevated due to benign prostatic hyperplasia, and adjustment for this phenomenon has been used to increase the specificity. PSA density is defined as PSA/prostate gland volume, and use of this PSA metric may predict which patients are at risk for extracapsular extension in the setting of a PSA <10 ng/mL [34]. Furthermore, Kang et al. demonstrated that for patients with a PSA between 4 and 10 ng/mL, adjustment of PSA for the volume of transition zone tissue may reduce unnecessary prostate biopsies [35].

Additional methods to increase specificity of PSA rely on the fact that PSA exists in two fractions in serum: complexed PSA, which is bound to plasma proteins, and unbound or free PSA. Jung et al. demonstrated that %free PSA could be used to distinguish between BPH-associated

elevated PSA and prostate cancer but could not be used reliably to differentiate between chronic prostatitis and prostate cancer [36]. In men with a PSA <2.5 ng/mL, %free PSA and DRE were shown to be the only reliable independent predictors of prostate cancer [37].

PSA alone has a limited ability to aid in the diagnosis of prostate cancer because of its low specificity. The discovery of free and complexed forms of PSA led to an increase in specificity for prostate cancer by demonstrating that the ratio of free to complexed PSA was inversely proportional to the risk of harboring prostate cancer. It was also observed that serum PSA is composed of a diverse array of PSA isoforms. Over the last decade, investigators have discovered several free PSA isoforms. Four free PSA isoforms have been well characterized: BPSA, [-5/-7] proPSA, [-4] proPSA, and [-2] proPSA. In 2003, Mikolajczyk et al. discovered that proPSA is associated with prostate cancer by showing that in the 4–10 ng/mL PSA range, an analysis of the receiver operating characteristic area under the curve 0.689 versus 0.637 for %free PSA and 0.538 for complexed PSA [38]. In the largest retrospective study to date, Catalona et al. studied 1,091 patients by concluding that [-2] proPSA or “pan” proPSA (total of -2, -4, -5, and -7 proPSA) expressed as a ratio of with free-PSA-improved specificity for prostate cancer in patients with a PSA range between 2 and 10 ng/mL. The ratio of panproPSA

to free PSA reduced the need for prostate biopsy by 21%, while %free PSA reduced the biopsy rate by 13%[39]. Although analysis of PSA isoforms has been shown in the literature to improve the specificity for prostate cancer, more evaluation is necessary before clinical application.

Individual Risk Assessment for Prostate Cancer

Prostate cancer risk calculators have been shown to be superior to PSA and DRE in deciding whom to biopsy. Thompson et al. evaluated 5,519 men from the placebo group of the PCPT who underwent prostate biopsy and had a PSA test and DRE within a year preceding the biopsy and at least two prior annual PSA tests [40]. Using logistic regression, four variables were found to be significantly associated with risk for prostate cancer: PSA, family history of prostate cancer, abnormal DRE, and a previous negative biopsy result. The strength of this risk calculator is that it is based on a large sample of patients across a wide spectrum of PSA levels. As such, the Prostate Cancer Risk Calculator allows a man to assess his individual prostate cancer risk threshold and decide whether or not to undergo a prostate biopsy. Depending on the patient’s personal risk tolerance, he can decide whether or not to pursue a prostate biopsy. Figure 2.4 shows the

Individualized Risk Assessment of Prostate Cancer

Enter Your Information

Race

Age

PSA Level ng/ml

Family History of Prostate Cancer

Digital Rectal Examination

Prior Prostate Biopsy

[Calculate Cancer Risk](#)

Adjusted Prostate Cancer Risk Calculators

BMI

PCA3

Finasteride

%freePSA

[-2]proPSA

%freePSA and [-2]proPSA

Useful Links for Prostate Cancer

[National Cancer Institute](#)

[American Cancer Society](#)

Other Individualized Risk Assessment Tools for the Family

[Breast Cancer](#)

[Colorectal Cancer](#)

[Lung Cancer](#)

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Fig. 2.4 Prostate cancer risk calculator (<http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>)

PCPT-based Prostate Cancer Risk Calculator, which can be accessed at <http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>. However, when counseling patients regarding the decision to undergo a prostate biopsy, it is important to understand the limitations of risk calculators. Vickers et al. analyzed data from five European and three United States cohorts of men undergoing prostate biopsy and concluded that reliance on a single cohort to determine risk of prostate cancer based on PSA can have significant variation when applied to other clinical cohorts [41].

Risk of Overdiagnosis and Overtreatment of Prostate Cancer

The frequency of overdiagnosis is related to the time that screening advances diagnosis of prostate cancer, which is defined as lead time. Given the natural history of prostate cancer, there is the potential to overdiagnose and overtreat a significant number of what would have been clinically indolent prostate cancers that were never destined to cause symptoms or contribute to a patient's death. Draisma et al. mathematically modeled prostate cancer detection and progression calibrated to Surveillance, Epidemiology, and End Results program data and also performed microsimulation screening analysis (MISCAN) of the United States and ERSPC Rotterdam data and concluded that among screen-detected cancers that would have been diagnosed, the estimated mean lead time was 5.4–6.9 years and overdiagnosis ranged from 23% to 42%, while MISCAN modeling predicted a mean lead time of 7.9 years and an overdiagnosis rate of 66% [42]. Welch and colleague analyzed SEER data for the period from 1986 to 2005 and noted that after the introduction of PSA-based screening in 1987, more than one million additional men were diagnosed and treated for prostate cancer [43]. The rate of prostate cancer diagnosis was particularly increased for men younger than 50 years. Lead time in the ERSPC was analyzed by Finne et al. [44]. Using a cutoff of 4 ng/mL, the mean lead time in the study population was 6.8 years, and overdiagnosis or detection of nonprogressive tumors may significantly contribute to lead time.

Overdiagnosis and overtreatment are arguably the most pressing problems associated with PSA-based prostate cancer screening. In the future, improved biomarkers may have a significant impact in reducing this problem.

Prostate Cancer Prevention Trial

In 2003, the Prostate Cancer Prevention Trial (PCPT) significantly expanded our understanding of prostate cancer across a broad range of PSA values and changed our perception about PSA [45]. The PCPT was a phase 3, randomized, double-blind, placebo-controlled trial to determine if daily finasteride could reduce the risk of prostate cancer over a 7-year period. A total of 18,882 men were randomized to either placebo or 5 mg of finasteride. Men underwent annual PSA and DRE. During the study, men with a PSA of ≥ 4.0 ng/mL or an abnormal DRE underwent prostate biopsy. All patients underwent an end-of-study sextant prostate biopsy if they had never been diagnosed with prostate cancer during the trial.

The PCPT markedly shifted our perception of PSA. Prior to the trial, the PSA test was considered a dichotomous test, either normal or abnormal. The PCPT demonstrated that there is no “normal” PSA and that prostate cancer exists at all PSA levels. It is now widely recognized that a high prevalence of prostate cancer exists at a PSA < 4.0 ng/mL [46]. While it had been known that prostate cancer incidence rates in the aging male population were quite high, it was assumed that these generally small tumors detected at autopsy were generally not found with prostate biopsies employing 6–12 cores [47]. In the PCPT, for the first time, a group of men all underwent prostate biopsy regardless of PSA level. In this study, 2,950 men in the placebo group that had a normal DRE and PSA, who had never had an abnormal DRE or PSA over the 7 years of the study, underwent an end-of-study biopsy, and 24.4% of men were found to have cancer on biopsy [46]. Further analysis demonstrated a 24.5% sensitivity for PSA using an upper limit of 4 ng/mL. Additionally, to achieve a 90% sensitivity for cancer detection, a PSA of approximately 1 ng/mL would be necessary [48].

The performance of PSA was found to be better for higher grade tumors, but a cut point of 4.0 ng/mL would still miss 60% of Gleason 7 or higher tumors [48].

ERSPC and PLCO

Two large randomized controlled trials designed to investigate the benefit of prostate cancer screening were published in March 2009. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was a multi-institutional study of 162,000 men randomized to PSA-based prostate cancer screening every 4 years versus no screening [7]. Different screening intervals and follow-up routines were used in different countries. The ERSPC may be viewed not necessarily as a single study with a common protocol but as an amalgam of different studies. This study concluded that PSA-based screening without DRE resulted in an absolute reduction of 0.71 prostate cancer deaths per 1,000 men after a follow-up period of 8.8 years. This study also concluded that PSA-based screening results in a 20% relative risk reduction in prostate cancer death. With an average follow-up of 8.8 years, there were 214 prostate cancer deaths in the screening cohort versus 326 in the control group. Therefore, in order to prevent one prostate cancer death within an initial 10-year period, 1,410 men would need to be screened with the number needed to treat would be 48. Additionally, the age group found to benefit the most from prostate cancer screening was restricted to the 55–69 age group, which benefited the most in mortality reduction. Additionally, after adjustment for nonattendance and contamination effects, Roobol and colleagues determined that PSA-based prostate cancer screening actually reduces the risk of dying from prostate cancer by 31% [49]. Hugosson and colleagues reported results of the Goteborg cohort of the ERSPC, which had a longer follow-up period and shorter screening interval of 2 years [50]. It would be expected that the benefits of screening should increase beyond the 10-year trial period, and indeed the authors concluded that with increased follow-up, PSA-based screening demonstrated a larger decrease in prostate cancer

mortality than was seen in the ERSPC trial. In order to prevent one death from prostate cancer, 293 men would have to be screened, significantly lower than reported by the ERSPC trial. Loeb et al. performed a thoughtful analysis of ERSPC data and concluded that number needed to screen (NNS) and number needed to treat (NNT) are highly sensitive to the time-dependent effect of screening on prostate cancer mortality, implying that with longer follow-up, it is likely that the NNS and NNT to prevent a death from prostate cancer will decrease [51].

The screening interval in the ERSPC was predominantly every 4 years, but the Belgium cohort, which consisted of 8,562 patients, had a much broader screening interval, from 4 to 7 years. Nelen et al. reported the effect of screening interval on the screening outcome in 1,660 men from the screening arm of the Antwerp ERSPC cohort with an average screening interval of 6.1 years with a mean follow-up time of 8.4 years [52]. Interval cancers were defined as clinically diagnosed prostate cancers between two screening visits, while aggressive interval cancers were defined as stage M1 or N1 or a Gleason score of 7 or higher or a WHO grade of 3. Compared to the Rotterdam and Goteborg cohorts, the Antwerp cohort had a higher incidence of interval cancers (50, 3.0%) versus 0.43% in Rotterdam and 0.7% in Goteborg. The aggressiveness of these interval cancers was low with 36% detected at clinical stage T1 and 34% with clinical stage T2. The authors concluded that a 6-year screening interval may miss some aggressive prostate cancers, while a 4-year screening interval may be more effective at diagnosing aggressive interval cancers.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial randomly assigned 76,000 men to annual PSA testing for 6 years and annual DRE for 4 years [53]. This study concluded that screening is associated with no reduction in prostate cancer mortality at 7 years. However, the control arm of this trial was significantly contaminated by PSA screening. Men in the control group were made aware of screening but were not actively screened. Forty-four percent of the study participant's arm had already undergone a PSA test within 3 years of study entry, which effectively prescreened the

control group and likely diluted the effect on mortality of PSA-based screening. Despite a common protocol at each site, the PLCO trial essentially compares a rigorously screened group versus a cohort screened less rigorously. Considering the power required to show a significant difference between the two groups, it is easy to see why the PLCO trial failed to show a screening benefit, as prostate cancer deaths in the screening cohort were 50 versus 44 in the control group. Additionally, the prostate biopsy rate in men with a serum PSA of >4.0 ng/mL or an abnormal DRE was only 40%. It is likely that a substantial number of significant prostate cancers remained undetected in the screening arm. The control group was further contaminated because a significant number of men underwent PSA testing during the trial. Additionally, the median follow-up of 7 years is likely not long enough to demonstrate a significant difference between the two groups. It is interesting to note that all causes of mortality increased in the screened cohort of the PLCO. It is possible that the risk of mortality related to treatment may increase as may be seen with hormonal ablation with increased risk of heart disease, stroke, and diabetes [54].

Both the ERSPC and the PLCO trial address the significant problem of overdiagnosis and attendant overtreatment. The rate of overdiagnosis is far higher than was previously estimated. The ERSPC provides justification for screening, although at a cost of overdetection, and highlights the need for a well-informed decision after careful counseling by the patient's physician. The ERSPC and PLCO also stress the need for a sensitive and specific biomarker to differentiate between indolent and virulent prostate cancer, which is urgently needed.

Side Effects from Treatment of Screen-Detected Prostate Cancer

The ERSPC reported a 20% reduction in prostate-cancer-specific cancer mortality at the 10-year time frame, but it is unclear if this reduction in mortality outweighs the morbidity of treatment.

Carlsson et al. reported treatment side effects in the Goteborg cohort of the ERSPC and concluded that the excess burden of treatment-related side effects after population-based screening may be regarded as relatively low when compared to the number of men saved from prostate cancer death [55]. In the Goteborg trial, the number needed to treat to prevent 1 prostate cancer death was 12, significantly lower than the overall 48 reported by the combined ERSPC results. Erectile dysfunction and urinary incontinence were both evaluated in patients undergoing radical prostatectomy, and the authors concluded that despite the high risk of erectile dysfunction and incontinence, the burden of these complications was relatively low in comparison to the lives saved from prostate cancer screening.

Future Biomarkers for Prostate Cancer Screening

Prostate cancer gene 3 (PCA3) was originally described in 1999. Bussemakers and colleagues analyzed mRNA expression patterns in normal versus prostate tumor tissue and concluded that PCA3 is a noncoding RNA and is highly overexpressed in 53 of 56 tumors [56]. After DRE, a voided urine is collected and measurement of PCA3 mRNA is measured and normalized to PSA mRNA which results in a PCA3 score. Marks et al. calculated PCA3 scores in 233 men prior to repeat biopsy after initial negative biopsy in men with a PSA >2.5 ng/mL and determined that a PCA3 score cutoff of 35 resulted in a receiver operating characteristic curve area under the curve of 0.68, while the serum PSA AUC was 0.52 [57]. Additionally, at PCA3 scores <5 , 12% of men were noted to have prostate cancer, and if the PCA3 score was >100 ng/mL, 50% of men were diagnosed with prostate cancer. In a prospective study of 533 men, Deras and colleagues calculated PCA3 score after a standardized DRE before prostate biopsy and observed that the probability of positive prostate biopsy increased directly with the PCA3 score [58]. Men with a PCA3 score of <5 had a positive biopsy rate of 14%. If the PCA3 score was more than 100, 69%

of patients were noted to have a positive biopsy. ROC analysis revealed that a history of prior negative biopsy did not influence the diagnostic accuracy of this test. Prostate volume was also not seen to influence the performance characteristics of PCA3. In the REDUCE trial, a subset of the placebo arm comprising 1,140 patients was evaluated with PCA3 at year 2 and year 4 prior to scheduled prostate biopsy [59]. PCA3 score performance characteristics were validated in the largest repeat biopsy study to date. The most interesting finding in this study was that PCA3 scores were predictive of repeat biopsy at year 4 and suggested that prostate biopsy at year 2 had missed tumors, while PCA3 had, in fact, detected their presence. Nakanishi and colleagues were able to demonstrate that tumor volume and Gleason score significantly correlated with PCA3 score and may be useful in predicting low volume tumors (<0.5 cc) [60]. De la Taille et al. evaluated PCA3 by studying more than 500 men scheduled for prostate biopsy with a serum PSA between 2.5 and 10.0 ng/mL [61]. Mean PCA3 scores were found to be significantly higher for men with a positive biopsy than those with a negative biopsy, 69.6 versus 31.0. A PCA3 cutoff score of 35 was found to have optimal sensitivity (64%) and specificity (76%), and men with a PCA3 score of 35 or higher had a 2.7-fold higher probability of a positive biopsy (64%) than those with a PCA3 score of less than 35 (24%).

Using a panel of kallikrein markers may reduce unnecessary prostate biopsies. In 2008, Vickers and colleagues demonstrated that using free PSA, intact PSA, and human kallikrein 2 (hK2) by studying the Goteborg cohort from the ERSPC and concluded that biopsies could be reduced by 57% using a 20% threshold of risk for prostate cancer [62]. Benchikh et al. independently validated this method to reduce unneeded prostate biopsies by analyzing the French cohort of the ERSPC in 2010 [63]. Again, using a 20% threshold of risk for prostate cancer, this study found that prostate biopsies could be reduced by 49.2% at a cost of 61 missed prostate cancers, the majority of which would be low stage and low grade. Vickers and colleagues again replicated this method to reduce the need for biopsy by

studying the Rotterdam cohort of the ERSPC and were able to reduce prostate biopsies by 51.3% at a relatively low cost of missing 12 high-grade cancers [64].

Early prostate cancer antigen (EPCA) and early prostate cancer antigen-2 (EPCA-2) were first reported by Getzenberg et al. [65]. EPCA, a nuclear structural protein, is found in prostate cancer tissue but not observed in benign prostatic tissue or benign prostatic hyperplasia tissue. Leman and colleagues studied 385 patients with PSA <2.5 ng/mL, PSA equal to or >2.5 ng/mL with a negative biopsy, BPH, organ-confined prostate cancer, non-organ-confined disease, and prostate cancer with PSA <2.5 ng/mL [66]. An epitope of EPCA-2 and EPCA-2.22 was set at a cutoff of 30 ng/mL and found to have a 94% sensitivity and a 92% specificity for men with and without BPH for prostate cancer. Additionally, EPCA-2.22 was highly accurate for differentiating between localized and extracapsular disease with an AUC of 0.89, while PSA demonstrated an AUC of 0.62. EPCA holds promise as a biomarker for prostate cancer screening but requires more study before a final conclusion can be made.

Hypermethylation of CpG islands has been associated with a variety of different tumors [67]. Several genes have been identified in prostate cancer that have undergone abnormal hypermethylation: GSTP1, APC, MGMT, RASSF1A, PTGS2, and RAR-beta [68–71]. Aberrantly hypermethylated GSTP1 is the most well-characterized biomarker for prostate cancer. Changes to GSTP1 are seen in 70% of high-grade prostatic intraepithelial neoplasia and 90% of prostate cancers, implying that GSTP1 hypermethylation is an early event in the carcinogenesis of prostate cancer [72]. Roupret and colleagues investigated aberrant promoter hypermethylation in prostatic fluid in 95 patients, of which 63 patients had pT1 prostate cancer, 31 patients with pT2, and 1 with pT3, as well as 38 controls [73]. A combination of four genes, GSTP1, RASSF1a, RAR-beta2, and APC, were found to be the best markers to differentiate between benign and malignant cases. Prostate cancer patients demonstrated a markedly higher degree of hypermethylation of these four genes, see Fig. 2.5. The sensitivity and specificity of the

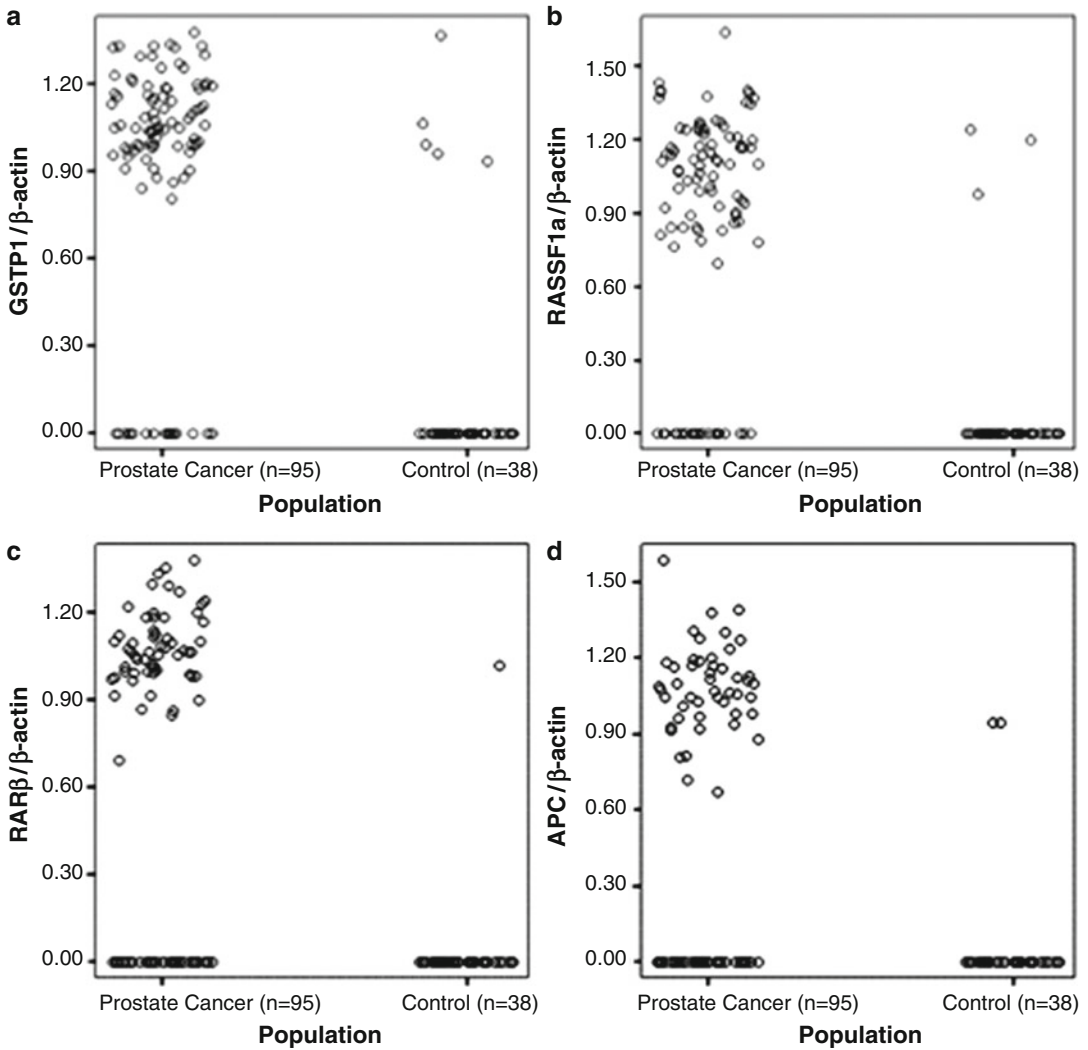


Fig. 2.5 Methylation levels of GSTP1, RASSF1a, RARbeta2, and APC in prostate cancer patients

four-gene set were 86% and 89%, respectively. Additional research into this area is underway, and future biomarkers for prostate cancer screening may include these potential biomarkers.

The most common type of fusion gene in prostate cancer is the fusion of TMPRSS2 and ERG. Perner et al. identified a significant association between higher stage tumors and TMPRSS2:ERG rearranged tumors [74]. This fusion gene has been found in approximately 50% of prostate cancers. Recently, Tomlins and colleagues investigated a urine-based assay for TMPRSS2:ERG rearrangement. In 187 prostatectomy patients,

TMPRSS2:ERG score positively correlated with markers of tumor volume, such as number of positive cores and maximum percentage of tumor involvement of a single core in the biopsy. Additionally, TMPRSS2:ERG score was also positively associated with maximum tumor dimension but was not associated with prostate weight, serum PSA, or PSA density. TMPRSS2:ERG score was additionally significantly higher in patients with high prostatectomy Gleason score and tumor upgrading at prostatectomy. Finally, TMPRSS2:ERG score was higher in men with significant versus insignificant cancer at

prostatectomy as well as biopsy. Tomlins et al. also combined PSA3 score with the TMPRSS2:ERG score to individualize prostate cancer risk and found that this combined score predicted risk of prostate cancer diagnosis and higher Gleason score. Urine assays for TMPRSS2:ERG score and PCA3 score may have utility in determining the urgency for biopsy and may individually risk stratify men. Further study is needed to determine the clinical utility of this new biomarker.

One method to reduce unnecessary prostate biopsies is to target patients at higher risk for prostate cancer. Lilja et al. analyzed blood samples from 21,277 Swedish men from the Malmö Preventive Project which was a cardiovascular study from 1974 to 1986 [75]. In Sweden, national guidelines advise against routine PSA-based prostate cancer screening and most prostate cancers are diagnosed clinically. This study concluded that a single PSA drawn at age 44–50 is a very strong predictor of prostate cancer clinically diagnosed decades later. These findings were not restricted to insignificant prostate cancers and pertain to clinically palpable and advanced or metastatic at diagnosis. The risk of clinically diagnosed prostate cancer was low (1–5%) for men with a PSA < 0.5 ng/mL and was 8–15% for men with a PSA of 0.75–1.25 ng/mL. For a PSA above 1.5 ng/mL, the risk of prostate cancer was significantly higher. The clinical implication of this study is that a single early PSA could be used to individualize later screening for prostate cancer. In men with a low initial PSA of less than the median (0.6 ng/mL), annual screening could be expected to be of little clinical benefit and, likewise, men with high initial PSA could be advised that they are at a significant increased risk for developing clinically significant prostate cancer. Risk stratifying prostate cancer screening could retain many of the benefits of screening such as reducing mortality while avoiding harm of unnecessary screening and overdiagnosis. Unfortunately, without appropriate screening biomarkers validated to separate indolent from aggressive prostate cancers, the phenomena of overdiagnosis and subsequent overtreatment will continue to be a problem.

Individualizing PSA values may lead to a decrease in overdiagnosis and overtreatment. Gudmundsson and colleagues analyzed six genetic loci and their association with PSA levels and risk of prostate cancer [76].

Prostate Cancer Screening Today

In 2009, the American Urological Association released a PSA Best Practice Statement [77]. Updated from 2000, this statement had two important changes:

- A recommendation that initial PSA-based prostate cancer screening begins at age 40
- A recommendation that no single threshold PSA value be used to trigger a prostate biopsy

The authors of this best practice statement concluded that all men at risk for prostate cancer should be counseled regarding the relative risks and benefits of prostate cancer screening. Additionally, improved biomarkers are urgently needed to improve the detection of clinically significant prostate cancers and reduce overdiagnosis and overtreatment of insignificant cancers.

The United States Preventive Services Task Force (USPSTF) has concluded that there is convincing evidence of harms of detection and early treatment [78]. The task force concluded that treatment for screen-detected prostate cancer causes moderate to substantial harms such as erectile dysfunction, urinary incontinence, bowel dysfunction, and death, especially since many screen-detected prostate cancers are never destined to cause symptoms or death of the patient and adequate evidence that screening causes pain and discomfort from a prostate biopsy as well as psychological effects from a false-positive test. Controversially, the USPSTF changed its previous position and recommended against prostate cancer screening in 2011.

The American Cancer Society (ACS) recommends that men make an informed decision with their health-care provider about prostate cancer screening after a careful consideration of the risks, uncertainties, and benefits beginning at age 50 in men with average risk for prostate cancer

and expected to live at least 10 years [79]. For men at high risk for prostate cancer, such as African-American men and men with a first-degree relative diagnosed with prostate cancer earlier than age 65, a discussion about screening should occur at age 45. For those men at an even higher risk, such as a man with several first-degree relatives with prostate cancer at an early age, a discussion about screening should occur at age 40. The recommended screening interval for a PSA <2.5 ng/mL should be every 2 years, and for those with a PSA >2.5 ng/mL, the interval should be annual.

Editorial Commentary:

No other topic in prostate cancer diagnostics generates as much controversy as screening. This exploded as this book was going to print based on the highly controversial position taken by the United States Preventive Services Task Force (USPSTF). Their interpretation of the published data led to a recommendation not to screen.

This position does have some justification based on a literal and narrow view of the published data, but in my (also controversial) opinion, it ignores the complexity of this issue. Most importantly, the large trials discussed in this chapter do demonstrate an undeniable and significant decrease in prostate cancer mortality when screening is performed. Furthermore, the impact is even more obvious when taking into account the decrease in mortality among men that actually were screened, regardless of group that they were randomized to. This is most likely related to the degree of cross-contamination in the groups, for example, that many men randomized to screening did not undergo screening, and of those, many with abnormal PSA did not undergo biopsy and/or treatment. Furthermore, larger numbers of men randomized to the non-screening arm actually did undergo screening outside the protocol either during or before the study periods, so their results cannot be considered controls representative of non-screening status.

Finally, the benefits of screening are clearly most influential over time based on the natural history of prostate cancer. Thus, follow-up studies from two of the ESRPC centers have now predictably shown that the benefit continues to become more exaggerated as the patients go

beyond 10 years, and the numbers needed to screen and treat become far more justifiable.

Thus, it becomes clear that screening is mostly beneficial for men with a life expectancy of over 10 years. Furthermore, a single PSA at some point in mid-life – 40 years is the AUA recommendation – serves as a significant predictor of future prostate cancer risk. If it is very low (<1.0 ng/dL), the patient is unlikely to develop prostate cancer in the foreseeable future. If it is even slightly elevated (>1.0 ng/dL) at that age, the patient should undergo serial evaluation and may require biopsy if it continues to rise.

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