Prostate-Specific Antigen Best Practice Statement: 2009 Update

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Abbreviations and Acronyms

ASTRO	=	American Society for Therapeutic Radiation and Oncology
AUA	=	American Urological Association
BPH	=	benign prostatic hyperplasia
cm	=	centimeter
CT	=	computed tomography
DRE	=	Digital Rectal Examination
ERSPC	=	European Randomized Study of Screening for Prostate Cancer
mg	=	milligram
mL	=	milliliter
MRI	=	magnetic resonance imaging
MRS	=	magnetic resonance spectroscopy
NCI	=	National Cancer Institute
ng	=	nanogram
PCPT	=	The Prostate Cancer Prevention Trial
PIN	=	Prostatic intraepithelial neoplasia
PSA	=	Prostate-specific antigen
PSADT	=	PSA doubling time
PSAV	=	PSA velocity
TURP	=	transurethral resection of the prostate
TZPSAD	=	PSA density of the transition zone
US	=	United States

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Abstract

Prostate cancer is the most common noncutaneous cancer in men in the United States (US). Despite its prevalence, the natural history of this disease is remarkably heterogeneous. In many patients, the cancer progresses slowly, resulting in tumors that remain localized to the prostate gland. Although potentially life-threatening, such cancers are most often curable. Many patients with low grade and volume cancers may be candidates for active surveillance. In other patients, however, tumor growth may be more rapid, resulting in cancer spreading beyond the confines of the prostate. In such cases, long-term survival may be considerably diminished compared to survival associated with organ-confined cancers. Strategies for managing prostate cancer have therefore been aimed at early detection, with selective, tailored treatment.

Prostate-specific antigen (PSA) is a tumor marker currently used for early detection of prostate cancer. Measurement of serum PSA levels has significant clinical application in other areas of prostate disease management. The purpose of this report is to provide current information on the use of PSA testing for: (1) the evaluation of men at risk for prostate cancer, (2) the risks and benefits of early detection (3) assistance in pretreatment staging or risk assessment, (4) post-treatment monitoring, and (5) use as a guide in management of men who recur after primary or secondary therapy. The report is an update of the previous American Urological Association (AUA) PSA Best Practice Policy 2000. There are 2 notable differences in the current policy. First, the age for obtaining a baseline PSA has been lowered to 40 years. Secondly, the current policy no longer recommends a single, threshold value of PSA which should prompt prostate biopsy. Rather, the decision to proceed to prostate biopsy should be based primarily on PSA and Digital Rectal Examination (DRE) results, but should take into account multiple factors including free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity,

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prior biopsy history and comorbidities. In addition, although recently published trials show different results with regard to the impact of prostate cancer screening on mortality, both suggest that prostate cancer screening leads to overdetection and overtreatment of some patients. Therefore, the AUA strongly supports that men be informed of the risks and benefits of prostate cancer screening before biopsy and the option of active surveillance in lieu of immediate treatment for certain men newly diagnosed with prostate cancer.

The following updated statement is based on a review of the current professional literature, clinical experience and the expert opinions of a multispecialty panel convened by the AUA. It is intended to serve as a resource for physicians, other health care professionals, and patients. It does not establish a fixed set of guidelines, define the legal standard of care or pre-empt physician judgment in individual cases. It is also recognized that this guideline will likely change in response to new information. The AUA will carefully monitor new developments in the field and revise these guidelines as necessary.

Introduction

PSA is a glycoprotein produced primarily by the epithelial cells that line the acini and ducts of the prostate gland. PSA is concentrated in prostatic tissue, and serum PSA levels are normally very low. Disruption of the normal prostatic architecture, such as by prostatic disease, inflammation, or trauma, allows greater amounts of PSA to enter the general circulation. Elevated serum PSA level has become an important marker of many prostate diseases – including benign prostatic hyperplasia, prostatitis, and prostate cancer, the focus of this document. Prostatic intraepithelial neoplasia (PIN) does not appear to raise serum PSA levels.[1,2]

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The Use of PSA for Early Detection of Prostate Cancer

Prostate cancer is the most common noncutaneous cancer in men in the US, and the second leading cause of male cancer mortality, accounting for an expected 28,660 deaths in 2008.[3] The natural history of this disease is remarkably heterogeneous and, at this time, is not clearly and consistently understood. An analysis of autopsy studies has shown that approximately one in three men over the age of 50 years had histologic evidence of prostate cancer, with up to 80% of these tumors being limited in size and grade and, therefore, clinically insignificant.[4, 5] A recent study of incidental prostate cancer diagnosed in organ donors found prostate cancer in 1 in 3 men age 60-69, and this increased to 46% in men over age 70.[6] Fortunately, the lifetime risk of prostate cancer death is only about 3%.[7]

Some studies have found that a large proportion of patients diagnosed with clinically localized prostate cancer who did not receive early aggressive treatment still had favorable clinical outcomes and normal life expectancies.[8-10] Most of these studies included an older population of men as well as a larger proportion of men with low-grade tumors. Although outcomes can be worse with extended follow up,[11] the general disparity between the high prevalence of prostate cancer and the relatively low lifetime risk of prostate cancer death highlights the importance of distinguishing those cancers that are destined to cause significant illness and premature death from those that are not.

PSA testing is one of several measures that can be used for the characterization and risk assessment of prostate cancer prior to therapy, as well as for the development of treatment recommendations (Figure 1). Other such measures include Gleason score, clinical stage, tumor volume as measured by biopsy, number of positive biopsy cores, extent of cancer within the

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cores, and imaging.[12-16] The use of PSA testing for the early detection of prostate cancer remains controversial, however, owing to its biological variability, high prevalence, and the strong evidence for overdiagnosis and overtreatment.[17, 18]

There has been a gradual but steady decline in prostate cancer mortality in the U.S. of approximately 30%.[19] This trend began fairly soon after the introduction of PSA testing, there is evidence from statistical modeling studies that PSA testing has played a role.[20-22] Screening with PSA is responsible for a substantial shift towards detection of prostate cancer at earlier stages.[23] Moreover, recent evidence from both a randomized trial in Sweden and a well-controlled cohort study in the U.S. indicate that active treatment of clinically localized prostate cancer may reduce prostate cancer specific mortality.[24, 25] Data from observational studies in the US and Austria also suggest an association between PSA screening and decreased prostate cancer specific mortality.[26, 27] These conclusions have not been supported in all studies, however. A recent randomized trial of prostate cancer screening with PSA, the European Randomized Study of Screening for Prostate Cancer (ERSPC), demonstrated only a modest 20 percent relative reduction in prostate cancer deaths among those screened when compared to those that were not at 9 years.[17] In this study, it was estimated that 1410 men would need to be screened and 48 men treated for prevention of one prostate cancer death over 10 years. Similarly, the Prostate, Lung, Colon, and Ovary Trial of the National Cancer Institute (NCI) found no difference in prostate cancer deaths at 7-10 years of follow-up when comparing those screened to those that were not.[28] The results of this study should be reviewed with some caution as acknowledged by the authors. Many men (approximately 44%) in the experimental and control groups had undergone PSA testing previously, before entry into the trial. Such pre-screening could have eliminated some cancers, which would have been detectable in the

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randomized population. Importantly, screening in the *control* group was very substantial (52% in the sixth year) which could have masked a modest impact of screening on mortality. Indeed, the level of screening in the control arm may have been higher as the vast majority of cancers detected were stage I or II at diagnosis. Such cancers are usually detected by PSA and/or DRE. Lastly, follow-up for both trials may not be long enough to detect a benefit for screening given the protracted natural history of many prostate cancers. Thus, it is still not clear that prostate cancer screening results in more benefit than harm. Longer follow-up in these randomized trials will be necessary to address the balance of benefits and harms of screening for prostate cancer. It should be pointed out that these trials used a single cut-point of serum PSA to prompt a biopsy, a different strategy than is proposed in these updated guidelines.

Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical. Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of overdetection and overtreatment should be included in this discussion. Because there is now evidence from a randomized, controlled trial regarding a mortality decrease associated with PSA screening, the AUA is recommending PSA screening, as proposed in this document, for *well-informed* men who wish to pursue early diagnosis. The AUA recommends that all discussions of treatment options include active surveillance as a consideration, since many screen-detected prostate cancers may not need immediate treatment.

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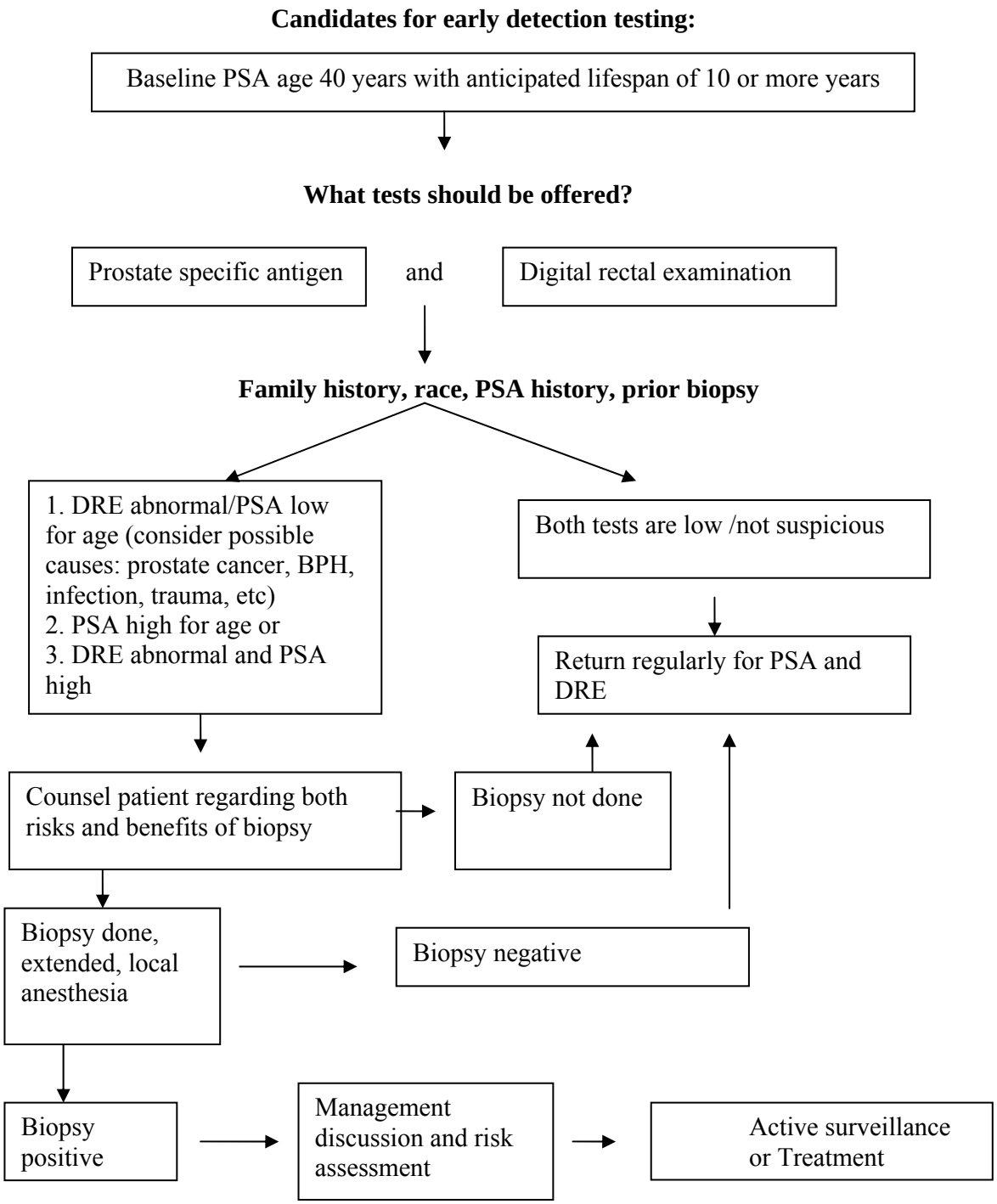

Figure 1: Early Detection

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1. The goal of early prostate cancer detection.

The goal of early detection is to reduce the overall morbidity and mortality of prostate cancer. The ERSPC trial has demonstrated that screening decreases the risk of being diagnosed with metastatic prostate cancer[29] and that screening is associated with a modest 20 percent reduction in prostate cancer deaths, albeit at a cost of overdiagnosis and overtreatment.[17] Studies have shown that long-term survival is considerably diminished in men diagnosed with prostate cancer that has already spread beyond the confines of the prostate to regional lymph nodes or to more distant sites. In general, the outcomes for such cases are less likely to be improved by therapy than lower volume or grade tumors, although patients with very advanced cancer benefit from treatment, often in combination with androgen deprivation.[12, 30]

2. The proportion of clinically significant prostate cancer detected with PSA is unknown.

There is currently no universally accepted definition of clinically significant or insignificant prostate cancer. Ideally, such a determination would be made using pretreatment variables, thereby facilitating an informed discussion that might obviate unnecessary or aggressive therapy in certain patients. Previous studies have focused on measures such as cancer volume, stage, and histologic grade.[31-35] More recently, investigators have shown that the number of biopsies showing cancer, as well as the extent of cancer in individual cores, may both be helpful in assessing the likelihood of insignificant disease.[36-38] Various risk assessment tools (i.e. nomograms, probability tables, etc) can also be used to help determine the likelihood of pathologic outcomes and recurrence free survival after treatment.[14-16, 39, 40]

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Tumor grade appears to be the strongest prognostic factor, although such assessments, even from multiple biopsy specimens, are subject to sampling errors.[31, 34] The most common system currently in use is the Gleason grading system.[41] The pathologist assigns a primary grade from 1 to 5, with 5 being the most aggressive, to the pattern occupying the greatest area of the specimen. A secondary grade is then assigned to the pattern occupying the second largest area. These two grades are added to determine the Gleason score, which ranges from 2 to 10. It is generally agreed that tumors with a Gleason score of 2 to 4 are very uncommon and have lower biological aggressiveness, while scores of 5 to 6 have an intermediate aggressiveness, and those with a Gleason score ≥7 or primary Gleason 4 or 5 are biologically aggressive tumors.[42] It should also be noted that Gleason 4/3 cancers are more aggressive than 3/4 cancers and such groups should not be combined.[43, 44] Some have suggested adding a "tertiary" grade,[45] especially since, in recent years, reported Gleason grades have encompassed a narrower range, and thus may have lost some of their prognostic value. Over time, the classification of Gleason grade by pathologists has changed, with contemporary Gleason scores being higher than those classified in the past. This is responsible for the rarity of tumors classified as Gleason sum ≤5.[46]

The volume of cancer that predicts clinical significance is of great debate. Many have defined tumor volume exceeding 0.5 mL to be clinically significant, although this is not well validated. Tumors with a volume between 0.5 to 1.9 mL are often, but not always, associated with higher PSA values and are more likely to progress if left untreated or exhibit spread beyond the prostate (extraprostatic disease).[47-49] No currently available noninvasive imaging method can consistently and reliably measure tumor volume.

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Epstein and colleagues suggested that 4 criteria could predict for the presence of insignificant cancer : tumor volume < 0.5 cm^3, PSA density <0.15, no pattern 4 or 5 Gleason grade disease, involvement of less than 3 mm of tissue, and involvement of only one needle core.[34] A recent European study highlights the fact that this grouping of aggressiveness is only a rough approximation, however, and found that these criteria can underestimate the aggressiveness of the tumor in up to 24% of cases.[50]

Due to the profound stage migration which has occurred as a result of widespread PSA screening, most men diagnosed with prostate cancer in the US each year will have clinically localized disease.[51-53] Whereas 19.2% of patients presented with locally advanced disease in 1988, only 4.4% of patients presented with clinical stage T3 or T4 a decade later.[54] Although poor prognostic features do not always indicate a poor outcome or ultimate death from the disease, they do correlate with a significantly greater chance of disease progression. Also of note, autopsy studies have found capsular penetration, lymph node spread, and poorly differentiated tumors in a limited number of patients with no clinical suspicion of prostate cancer.[55]

Accumulated data suggest that combinations of preoperative data, including PSA level, clinical stage, and Gleason score from biopsy, can significantly enhance the ability to predict actual pathologic stage and outcome following treatment.[14-16, 56]

3. Men who wish to be screened for prostate cancer should have both a PSA test and a DRE.

Researchers agree that the introduction of PSA testing led to a dramatic increase in the number of men diagnosed with prostate cancer, with peaks in 1991 for men over age 65 and in 2002 for

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men under age 65.[3, 57] Subsequently, prostate cancer incidence rates in the US have fallen somewhat, but they are still twice the rates recorded prior to the introduction of PSA testing. Most prostate cancers detected in the US are identified on the basis of PSA testing.

Prior to 1987 (pre-PSA era), as many as 35% of all patients with apparent clinically localized disease were found to have positive lymph nodes at surgery, and two-thirds were found to have pathologically advanced disease.[58, 59] As a consequence of PSA testing, there has been a significant stage shift in favor of localized disease.[60, 61] Forty eight percent of prostate cancers diagnosed in the US today are clinical stages T1a to T1c, and 85% are clinically localized at the time of diagnosis.[19]

While PSA level measurement is currently the best single test for early prostate cancer detection, DRE can also identify men with the disease. Evidence from three uncontrolled studies suggests that combining both tests improves the overall rate of prostate cancer detection when compared to either test alone.[62-64] Recent evidence from the ERSPC found that DRE did not improve prostate cancer screening over PSA testing alone, however.[65] Finally, DRE examination may be a barrier to screening for some.[66] Transrectal ultrasonography adds no additional information to the combination of PSA testing and DRE as screening tests, but is useful in biopsy guidance and staging.[9, 67]

The widespread use of PSA testing has caused many men to be diagnosed with prostate cancer much earlier in their lives when compared to the pre-PSA era. Gann et al originally estimated that the mean lead time associated with PSA testing was 5.5 years.[68] More recently, Draisma et

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al published a model based on data from the ERSPC suggesting that prostate cancer diagnosis was advanced by as much as 10 years among men aged 55, and by five years for men aged 75.[69]

Unfortunately, prostate cancer poses an epidemiologic conundrum. Recent studies have shown that the lifetime risk of prostate cancer diagnosis is about 16%, but the lifetime risk of dying from this disease is only 3.4%.[19] Thompson et al reported an extraordinarily high prevalence of prostate cancer among 2950 healthy men participating in a prostate cancer chemoprevention study comparing finasteride versus placebo.[70] All of these men had PSA levels below 3.0 ng/mL at the start of the study, and all of the men studied had PSA levels that remained below 4.0 ng/mL during the seven years of follow-up. Remarkably, 6.6% of the men whose PSA measured less than 0.5 ng/mL had prostate cancer, and 26.9% of the men with PSA levels between 3.1 and 4.0 ng/mL had prostate cancer. Thus, of these men, whose PSA was previously thought to be 'normal', 15% were found to have cancer. However, it remains unknown what proportion of these cancers includes clinically significant disease.[71]

These findings highlight a difficult paradox. A significant proportion of men harbor small foci of latent prostate cancer, many of which are not destined to become clinically significant. Widespread, repeated PSA testing has raised a concern over the possible overdetection of prostate cancer. Overdetection refers to the ability of a screening test to identify a condition that would have remained silent and caused a patient no morbidity during his lifetime. This is in contrast to overtreatment, although in the US these two are unfortunately often linked, in some cases to the detriment of patient quality of life. For example, despite a decrease in risk category of disease at the time of diagnosis, approximately 90% of men still elect some type of intervention, including surgery, radiation therapy, or androgen deprivation.[52] Epidemiologists

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have long known that the initial use of a screening test in a population will more frequently identify relatively slow growing tumors as compared to aggressive tumors. This is often referred to as length time bias. With repeated testing in a population, this length bias diminishes, and diminishes at a faster rate when intervals between repeat tests are shorter. However, the likelihood of detecting smaller, more indolent tumors that will never progress to clinical significance remains high. Draisma et al have estimated that at age 55 years, PSA testing results in an overdetection rate of 27%.[69] By age 75, the rate of overdetection increases to 56%. Similar concerns have been raised by others.[72, 73]

Although testing for PSA involves obtaining only a blood test, several subsequent events must be considered before the test can be considered innocuous. A positive test result affects patients both mentally and physically even if a patient chooses not to proceed to prostate biopsy.[74] In most instances, a positive test leads to a transrectal ultrasound and prostate biopsy. Although the procedure is uncomfortable, it is well tolerated by most men and usually is performed as an office procedure, often under local anesthesia. The risks of biopsy are small but not insignificant. Significant bleeding and infection occur in 1% to 4% of patients who undergo biopsy.[75-77]

Although the psychological stress of diagnosis alone cannot be overlooked, most of the morbidity associated with PSA testing is related to the treatment procedures currently available to those found to have prostate cancer,. In men with clinically significant prostate cancers, complications associated with treatment are most often considered acceptable if the treatment prolongs life or reduces morbidity from the disease. In men who harbor indolent disease or disease that is not likely to become symptomatic during the patient's lifetime, however, any

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morbidity from treatment likely lowers quality of life and should be considered a potential harm associated with PSA testing. Problems include urinary, bowel, and erectile dysfunction, as well as emotional distress and anxiety due to a cancer diagnosis and subsequent decision making and treatment.[78]

4. A variety of factors can affect PSA levels and should be considered in the interpretation of results.

The three most common prostatic diseases – prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer – can all be associated with elevated serum PSA levels. Treatment with antibiotics will decrease PSA by approximately 30% in men whose PSA elevation is due to prostatitis alone.[79, 80] Other factors that are known to cause elevations in PSA levels include urethral or prostatic trauma, and infection.[81, 82] It is therefore important to take a careful medical history prior to assessing the PSA value in a patient. Surgical castration or medical castration (with LHRH-agonist or antiandrogen therapy) will often lower PSA levels dramatically. Finasteride (5 mg dose) and dutasteride (.5 mg dose), 5-alpha reductase inhibitors used for the treatment of BPH and male pattern baldness (1 mg dose of finasteride), will lower PSA levels by approximately 50% regardless of the dose.[83] For screening purposes, PSA levels should be adjusted in patients taking 5-alpha reductase inhibitors to estimate the true PSA level. In the The Prostate Cancer Prevention Trial (PCPT) trial men receiving finasteride for less than four years, a PSA multiplier was employed. At the beginning of a patient's fourth year on the drug, the PSA level was multiplied by 2.3 from then onward.[84]

Ejaculation and DRE have been reported to increase PSA levels but studies have shown the effects to be variable or insignificant.[85, 86] For this reason, PSA testing can be performed with

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reasonable accuracy after rectal examination. Prostate biopsy, however, will usually cause substantial elevation of PSA levels. PSA testing should be postponed for at least three to six weeks due to this effect.[87] Cystoscopy may increase PSA levels immediately after testing, although results remain contradictory.[87-92] Hemodialysis and peritoneal dialysis have not been found to alter total serum PSA levels significantly; therefore, total serum PSA levels of patients with end-stage renal disease need no adjustment.[93-95] Free serum PSA is altered by hemodialysis and should not be used for screening in these patients.

Lastly, short term fluctuations in PSA, due to one of the reasons given above, or to simple laboratory variability, can lead to inappropriate biopsy and potential overdetection of indolent or small-volume cancer. Laboratory variability can range from 20-25% depending upon the type of standardization used. Assays using the 1999 World Health Organization standard yield results 20-25% lower than those using the Hybritech® standard. For this reason, it is important for physicians and patients to know which assay was used and to use the same assay for longitudinal monitoring. PSA assays are not interchangeable and there is no acknowledged conversion factor between them.[96-98] Therefore, consideration should be given to confirming an abnormal PSA before proceeding to biopsy. This is especially true if a normal DRE is combined with either low, but abnormal PSA levels (i.e. <5 - 6 ng/mL), or with abnormal, but limited fluctuations in PSA at low levels (i.e. abnormal change in velocity with normal, baseline total PSA level). DRE screening may also produce serendipitous findings of prostate cancer if a biopsy is positive from a region other than the one felt to be abnormal.[99-100]

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5. For patients choosing to undergo PSA testing, several important questions arise regarding the PSA test's performance for detection of prostate cancer.

PSA testing in patients with a serum PSA level above 4.0 ng/mL has a sensitivity of about 20% in contemporary series.[101] One way to improve sensitivity of PSA is to use a lower threshold value for all men. Doing so improves the likelihood of detecting cancers, including some aggressive tumors that are present at PSA levels below 4.0 ng/mL, but also risks the detection of clinically-insignificant tumors. Another way to improve sensitivity is to adjust the "threshold" PSA level to a lower value for younger men (age-specific or age-adjusted PSA). Men in their 40s that are cancer-free, for example, most likely have a serum PSA value of 2.5 ng/mL or less.[102]

Assessment of PSA kinetics, PSA doubling time (PSADT) or PSA velocity (PSAV), has been used to assess both cancer risk and aggressiveness. PSAV is primarily used to detect prostate cancer, whereas PSADT is primarily used in the post treatment setting as a surrogate marker of outcome. Some investigators have suggested that a PSA rise of 0.75 ng/mL or greater in a year is reason for concern in patients with a PSA level >4.0 ng/mL.[103] While a PSAV of 0.75 ng/mL per year has been recommended for men with PSA values between 4-10 ng/mL, several studies suggest that lower PSAV thresholds of 0.4 ng/mL per year may improve prostate cancer detection for younger men and for those with PSA levels below 4.0 ng/mL.[40, 104-106] To correctly measure PSAV, use of at least three PSA values over a time period of at least 18 months is recommended.[40, 106] Estimating PSAV with values spread over a longer interval is problematic because when significant prostate cancer is present, PSA increases exponentially and a linear estimate of PSA slope is less valid. The problem of using linear regression to estimate the slope of an exponentially rising PSA can be easily overcome by calculating an average PSAV between 3 measures (the annualized PSAV between the first 2 measures plus the annualized PSAV

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between the second 2 measures divided by 2). Some have suggested that PSAV cutpoints should be lowered and age adjusted. Age-adjusted PSA velocities with threshold values of 0.25 ng/mL/yr in men ages 40 to 59, 0.5 ng/mL/year in men ages 60 to 69, and 0.75 ng/mL/year for men over 70 years of age have been propose.[104] Both age-specific PSA and age-specific PSAV will increase the number of cancers detected, and both will also increase the number of younger men undergoing biopsy. However, when added to total PSA, PSAV was not shown to be a useful independent predictor of positive biopsy, in the ERSPC and PCPT trials, or in other analyses.[97, 107, 108.]

The specificity of PSA testing is approximately 60% to 70% when the PSA cutoff level is >4.0 ng/mL.[109] Several methods have been suggested to increase PSA specificity for prostate cancer and thereby reduce the number of unnecessary biopsies. Only about one prostate biopsy in four currently finds prostate cancer.[110] One method to improve PSA specificity is to set higher "normal" PSA levels for older men. Because serum PSA tends to increase with age, the use of higher "normal" levels for older men results in fewer biopsies.[111] Some evidence suggests that the use of age adjusted PSA increases the risk of missing high grade cancers in older men, and may overdetect smaller volume/lower grade tumors in younger men.[112] Table 1 shows several published "normal" age ranges for PSA, based upon the ethnic background of the patient. As a reference, age-specific, median PSA values are 0.7 ng/mL for men in their 40s, 0.9ng/mL for men in their 50s, 1.2 for men in their 60s, and 1.5 for men in their 70s.[113]

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Table 1. Age-Specific Reference Ranges for Serum PSA[111]			
	Reference Range		
Age Range	**Asian-Americans**	**African-Americans**	**Whites**
40-49 yr	0-2.0 ng/mL	0-2.0 ng/mL	0-2.5 ng/mL
50-59 yr	0-3.0 ng/mL	0-4.0 ng/mL	0-3.5 ng/mL
60-69 yr	0-4.0 ng/mL	0-4.5 ng/mL	0-4.5 ng/mL
70-79 yr	0-5.0 ng/mL	0-5.5 ng/mL	0-6.5 ng/mL

Other methods of improving PSA specificity take advantage of the fact that PSA exists in the blood in two fractions, one bound to plasma proteins (complexed) and the other in a free state. Benign prostate tissue contains more free PSA than prostate cancer tissue. Patients with prostate cancer tend to have lower free/total ratios, whereas men with benign disease have higher free/total ratios, except in the case of prostatitis.[114] Using the ratio of free/total PSA will reduce the number of biopsies in men with serum PSA levels between 4.0 and 10.0 ng/mL.[115, 116] A recent meta-analysis of the performance characteristics of free/total PSA ratio concluded that only under certain defined situations does this ratio contribute more effectively as an adjunct to primary prostate screening with total PSA.[117] It appears from this analysis that percent free PSA adds modest clinical value in the 4.0 to 10.0 ng/mL total PSA range only when percent free PSA appears at extreme values, i.e., less than 7% to 10% and higher than 20% to 25%.[115-118] When free PSA is less than 7% to 10%, the sensitivity is approximately 40% and the specificity ranges between 72% and 92%. The performance characteristics can be significantly altered by utilizing a threshold of 20% to 25%, providing a sensitivity between 90% and 95%.

Some studies have assessed the use of complexed PSA as an alternative test to total PSA for early prostate cancer detection.[119-122] The majority of studies report an increased specificity and thus a decrease in the number of unnecessary biopsies utilizing complexed PSA in the total PSA

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range of 2.5 to 6.0 ng/mL. Equivalency for complexed PSA at higher total PSA levels up to 10.0 ng/mL has been reported, as well as equivalency between the ratios of free and complexed PSA to total PSA. The optimal cut-off points which would prompt a biopsy, whether for free/total PSA or for complexed PSA, are not known with certainty at present.[123]

Adjusting for total prostate or transition zone volume may improve PSA specificity. Since larger prostates produce larger amounts of PSA, adjusting the normal value for the size of the prostate (PSA density = PSA/gland volume) can reduce the number of biopsies performed.[124, 125] Additionally, compared to total PSA, PSA density of the transition zone (TZPSAD) may have increased specificity for prostate cancer when sensitivity is held constant.[121] When sensitivity is varied, TZPSAD of 0.37 ng/mL can identify prostate cancer better than free/total PSA in men with total PSA levels between 4.0 and 10.0 ng/mL.[126] Historically, however, the decrease in biopsies using PSA density has been associated with a decrease in cancer detection.[127] In addition, use of either PSA density or TZPSAD requires the use of transrectal ultrasound, which is costly and may not have acceptable inter-operator reproducibility, especially for TZPSAD.

All four methods – age-adjusted PSA, free/total PSA ratio, complexed PSA, and PSA/TZPSAD density – can be used to improve the sensitivity (detect more cancers) and/or specificity (avoid unnecessary biopsies) of PSA testing. To what extent such methods will do either is heavily dependent on the cut-points used and the subset of PSA levels to which they are applied.

The use of risk assessment tools can also be applied to prostate cancer screening and help determine the need for biopsy. Several nomograms help estimate a man's risk of harboring prostate cancer at different PSA levels, and recently a risk calculator was published that uses individual patient characteristics to predict his likelihood of having prostate cancer detected on

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biopsy.[128-131] These tools take into account multiple patient variables to help determine the need for prostate biopsy, rather than relying on an arbitrary threshold value, and facilitate discussion of a patient's individualized risk.

Because of potential tradeoffs between sensitivity and specificity, there is at present no consensus on optimal strategies for using the different modifications of PSA testing.

6. When is a prostate biopsy indicated?

Although an abnormal DRE or an elevated PSA measurement may suggest the presence of prostate cancer, cancer can only be confirmed by the pathologic examination of prostate tissue. The Prostate Cancer Prevention Trial had demonstrated that there is no safe PSA value below which a man may be reassured that he does not have biopsy-detectable prostate cancer. Instead, there is a continuum of risk at all values, with higher values of PSA associated with a higher risk of prostate cancer (Table 2). Because of this, the AUA is not recommending a single threshold value which should prompt prostate biopsy. The decision to proceed to prostate biopsy should be based primarily on PSA and DRE results but should take into account multiple factors, including free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history and comorbidities. This is because the use of a specific PSA cutpoint in combination with DRE alone can lead to an overestimation of risk in some and underestimation in others.[132] Therefore, individualized risk assessment based on a variety of risk factors, as mentioned above, may be a more appropriate way to characterize the risk, not only of prostate cancer, but also of "significant" prostate cancer, in an individual patient. Some have estimated risk informally or intuitively, whereas others have adopted formal risk calculators as described above. It should

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also be acknowledged that there are likely to be other serum markers, which will, in the future, either replace or complement the use of serum PSA for prostate cancer early detection.[133-138]

Prostate tissue for diagnosis of prostate cancer can be obtained in several ways. The most common method is by means of a transrectal, ultrasound-guided prostate biopsy, which is usually performed as an outpatient procedure with local anesthesia. A standard biopsy scheme is performed, consisting of at least 8 to 12 cores of tissue targeting the peripheral zone at the apex, midgland, and base, as well as laterally directed cores on each side of the prostate. In cases where extended or saturation biopsy schemes are indicated, additional tissue may be taken from the anterior and transition zones of the prostate as well. Standard biopsy schemes have been proven to identify more cancer at initial biopsy compared to sextant biopsies (6 biopsies taken bilaterally at the apex, midgland and base), decreasing the false negative rate from 20% to 5%.[139] After biopsy, blood in the stool or urine is common but usually disappears after a few days. Blood in the semen can be seen for up to several months after biopsy. Infections requiring prolonged antibiotics are uncommon and occur in less than 4% of biopsies.[75-77] Saturation biopsy, taking tissue from more than 20 locations, may be considered in men with persistently elevated PSA levels and multiple previous negative prostate biopsies.[140-142] An alternative to the transrectal saturation biopsy approach is transperineal prostate biopsy, which is performed under local, regional, or general anesthesia using a brachytherapy grid and transrectal ultrasound guidance. Like transrectal saturation biopsy, this technique is reserved for patients with elevated and/or rising PSA values and prior negative transrectal prostate biopsies. Percent positivity with transperineal biopsy ranges from 37% to 43%.[143, 144]

It is important to note that as the presence of prostate cancer cannot be excluded on the basis of

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ultrasonography alone, there is no role for transrectal ultrasound by itself in screening for cancer. Color Doppler ultrasound has been shown to have the potential for improving biopsy targeting, but, like gray scale, does not substitute for a biopsy.[145, 146] If a biopsy is indicated, based on the criteria described previously, the biopsy should be performed irrespective of a "normal" transrectal ultrasound examination.

Occasionally, prostate cancer may be detected when tissue is removed from the central portion of the prostate, usually during surgery for BPH. Tissue may be removed transurethrally during transurethral resection of the prostate (TURP) or through a transabdominal approach for larger prostate glands. In these cases, prostate cancer is generally an incidental finding as it is usually unsuspected prior to surgery. Of note, there are no data to support the idea that a TURP lowers the risk of developing prostate cancer. Transurethral resection of the prostate in men with negative transrectal biopsies, but persistently abnormal serum PSA levels, is rarely employed as an early detection strategy.[147]

Table 2. A continuum of prostate cancer risk exists even at traditionally low prostate-specific antigen (PSA) values.[70]

Relationship of PSA Level to Prostate Cancer Prevalence and High-Grade Disease.*

PSA Level	No. of Men (N-2950)	Men with Prostate Cancer (N-449) *no. of men (%)*	Men with High-Grade Prostate Cancer (N-67) *no./total no. (%)*
≤0.5 ng/mL	486	32 (6.6)	4/32 (12.5)
0.6-1.0 ng/mL	791	80 (10.1)	8/80 (10.0)
1.1-2.0 ng/mL	998	170 (17.0)	20/170 (11.8)
2.1-3.0 ng/mL	482	115 (23.9)	22/115 (19.1)
3.1-4.0 ng/mL	193	52 (26.9)	13/52 (25.0)

*High-grade disease was defined by a Gleason score of 7 or greater. The population above was restricted to men with a PSA level of 4.0 ng per milliliter or less throughout the study.

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7. The serum PSA level is generally proportional to the risk of prostate cancer, the extent of the cancer, and the long-term outcomes after treatment of the cancer.

In addition to the two previously stated questions (Section 5) that might be asked by a man undergoing PSA testing for prostate cancer, there is a third even more basic question: "What is the likelihood that I have prostate cancer if I have a high PSA?" The answer depends on the level of serum PSA and the rate at which it is rising

The average man older than age 50 years with a nonsuspicious DRE has about a 10% likelihood of having biopsy-detectable prostate cancer if his serum PSA level is 0.0 to 2.0 ng/mL; 15% to 25% if the PSA level is 2.0 to 4.0 ng/mL; 17% to 32% if the PSA level is 4.0 to 10.0 ng/mL; and 43% to 65% if the PSA level is above 10.0 ng/mL.[70, 116, 148, 149] Thus, there is no PSA level below which a man can be reassured that prostate cancer does not exist. Because of this, the use of risk assessment tools is an attractive alternative to a traditional threshold value.

Men with prostate cancer have higher PSAV values than those without prostate cancer.[103, 104, 150-152] On average, men without prostate cancer have a PSAV below 0.1 ng/mL/year,[103 150, 151] and the risk that prostate cancer is present increases directly with PSAV.

The PSA level and the rate at which it is rising are related to the extent and biological potential of prostate cancer. The proportion of men with higher volume cancers, extraprostatic disease, higher grade disease, and biochemical failure after treatment all increase as the PSA level increases.[129, 152-157] The proportion of men with pathologically organ-confined disease is about 80% when the PSA level at diagnosis is <4.0 ng/mL; about 70% when the PSA level is between 4.0 and 10.0 ng/mL; and about 50% when the PSA level is >10.0 ng/mL.[153, 154] In addition, the

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proportion of men with metastases to the pelvic lymph nodes is around 5% when the PSA level at diagnosis is 10.0 ng/mL or less, 18% when the PSA level is between 10.0 and 20.0 ng/mL, and 36% when the PSA level is above 20.0 ng/mL.[155, 158]

Extended lymph node dissection may identify a greater number of positive nodes, even at lower PSA values.[159, 160] Furthermore, even after accounting for age, race, grade, stage, and year of surgery, the preoperative PSA level is significantly associated with the risk of biochemical failure after surgical treatment of prostate cancer; for each 2-point increase in PSA level, the risk of biochemical progression increases by approximately 2-fold.[161] Biochemical recurrence of cancer is evident within 10 years of surgery in approximately 10% of men with a preoperative PSA level below 2.6 ng/mL, 20% when the PSA level is between 2.6 and 10.0 ng/mL, and 50% when the PSA level is above 10.0 ng/mL.[156, 157 161] Numerous investigators have found that the integration of clinical stage, histologic tumor grade, and PSA level can further refine the ability to predict outcomes after treatment for prostate cancer.

The PSAV prior to treatment of prostate cancer is also associated with the risk of prostate cancer death after treatment.[40, 106] When compared with men with a PSAV of 2.0 ng/mL/year or less in the year before diagnosis, men with a PSAV above 2.0 ng/mL/year may have an approximate10-fold greater risk of death from prostate cancer in the decade after radical prostatectomy.[40] However, with longer follow-up, these conclusions could change. In an unselected cohort of men participating in the Baltimore Longitudinal Study of Aging, a PSAV above 2.0 ng/mL/year in the 2 years prior to diagnosis was associated with a similar risk of prostate cancer death, compared to a PSAV of 2.0 ng/mL/year or less. However, 10 to 15 years before diagnosis (when most men had PSA levels below 4.0 ng/mL) PSAV was associated with cancer-specific survival

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25 years later; cancer specific survival was 92% among men with PSAV of 0.35 ng/mL/year or less, and 54% among men with PSAV above 0.35 ng/mL/year.[106]

8. The decision to use PSA for the early detection of prostate cancer should be individualized. Patients should be informed of the known risks and the potential benefits.

Prostate cancer mortality has recently been declining in the US. Analyses of this and other recent trends in prostate cancer rates suggest that a number of factors may be responsible, one of which may be the widespread use of PSA screening for the purpose of early detection.[20] Based on a randomized trial of prostate cancer screening, there appears to be a modest reduction in prostate cancer mortality among those screened when compared to those that are not.[17] In another screening study, there was no difference in prostate cancer mortality when comparing men that were and were not screened.[28] However, there is a large amount of overdiagnosis and overtreatment associated with screening[17, 28] and at this point it is not possible to state that screening is associated with more benefit than harm.

Advanced prostate cancer is associated with significant morbidity and mortality, including bone pain, inanition, anemia, ureteral obstruction, and bone fractures. In addition, treatments that are used to cure or slow the disease, or to ameliorate its complications, also have associated toxicities. Active treatment procedures, such as surgery (radical prostatectomy), radiotherapy (external beam radiation or interstitial prostate brachytherapy), cryotherapy or high-intensity focused ultrasound for localized prostate cancer; all carry a risk of complications. Potential complications of active treatments include erectile dysfunction, urinary incontinence or bother, and gastrointestinal symptoms. The AUA Prostate Cancer Guidelines recently reported a meta-

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analysis of symptoms in published literature after prostatectomy, external beam radiation, and interstitial brachytherapy.[162]

Decisions regarding early detection of prostate cancer should be individualized, and benefits and consequences should be discussed with the patient before PSA testing occurs. Not all men are appropriate candidates for screening efforts for this disease. Ideally, physicians should consider a number of factors, including patient age and comorbidity, as well as preferences for the relevant potential outcomes. Screening in men with less than a 10-year life expectancy, either due to age or comorbidity, is discouraged.[162, 163] Some organizations have even recommended that informed consent should be obtained prior to PSA testing.[164]

9. Early detection and risk assessment of prostate cancer should be offered to asymptomatic men 40 years of age or older who wish to be screened with an estimated life expectancy of more than 10 years.

Specialty groups (American Urological Association and American Cancer Society) have recommended that early detection begin at age 50 years for men at average risk of prostate cancer, and sooner for those men at higher life time risk (positive family history in a first-degree relative, African American race). Although family history of prostate cancer confers a higher risk of prostate cancer diagnosis, it is not associated with an increased risk of high-grade disease. Among men in their 40s and 50s, a baseline PSA level above the median value for age is a stronger predictor of future risk of prostate cancer than family history or race.[165, 166] One way to identify this high-risk group of men with a PSA level above the median value in their 40s is to obtain a baseline PSA level at age 40, and then to determine future screening intervals based upon this number. Men in their 40s with a PSA value above the median (0.6 to 0.7 ng/mL) are at

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higher risk for prostate cancer.[165, 166]

Although prostate cancer prevalence is low among men less than 50 years of age, there are a number of reasons to offer early detection prior to age 50. First, the age adjusted mortality rate for prostate cancer per 100,000 males (all races) between ages 55 and 64 is 18.[19] Since death from prostate cancer occurs, on average, 15 to 20 years after diagnosis of an early cancer, [11, 167] men dying at age 55 to 64 likely could have been cured by diagnosis and effective treatment prior to age 50. Second, when compared to men more than age 50, younger men are more likely to have curable prostate cancer.[168-170] Third, measurement of the PSA level is a more specific test for cancer in younger men compared to older men because prostatic enlargement is less likely to confound the interpretation of the estimated PSA value.[171] Fourth, infrequent testing of men in their 40s and after age 50 might reduce prostate cancer mortality and the cost of screening when compared to annual testing beginning at age 50.[172] Finally, given the relationship between PSAV and death from prostate cancer decades later, [106] establishing baseline PSA values against which to compare future PSA measurements after age 50 could help identify those men with life threatening prostate cancer at a time when cure is still possible.

The recommendation to perform PSA testing annually among men who decide to be tested is also not evidence-based. However, there is strong evidence that rescreening intervals should be based on the results of the PSA test since the future risk of prostate cancer is closely related to the PSA level.[68, 165 166, 173] For example, a screening interval of two years for men with PSA levels of 2.0 ng/mL or less is unlikely to miss a curable cancer.[174] Furthermore, recent analyses from sections of the European Randomized Study of Prostate Cancer Screening suggest that most cancers detected at two to four years after an initial screen (1st round) will be curable.[175-179] Because of the long natural history of prostate cancer and the ability of PSA screening to

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uncover most cases of advanced life-threatening cancer at the initial screen, frequent screening will contribute to the cumulative risk of undergoing a biopsy and appears unnecessary for most men.

PSA screening is common among the elderly more than age 70 with limited life expectancies,[163] and, in fact, more common among men more than age 70 than in men in their 50s.[180-182] Because of the long natural history of most prostate cancers and competing causes of death,[183] the benefits of screening may decline rapidly with age.[184, 185] For example, among older men over age 65 who were detected with low- to intermediate-risk prostate cancer in the PSA era, 200 men would need to be treated over 12 years to prevent one prostate cancer death.[25] Conversely, the median age of death from prostate cancer in the US is 80. A physician should assess the individual patient's health status to determine the appropriateness of PSA testing at any given age. Recently, the U.S. Preventative Services Task Force issued guidelines which recommend against screening men over age 75.[182]

While this recommendation estimates the age at which the average American male has ten years or less life expectancy, individualization of this recommendation is warranted, especially in men with excellent health, absence of comorbidities, and family longevity. The incidence of high - risk prostate cancer in fact increases with age, accounting for 43% of cancers diagnosed in men >75 vs. 25% among men <75.[186] Additionally, there must be a distinction made between screening for prostate cancer and treatment of prostate cancer. Diagnosis of prostate cancer in this age group may be informative for a man's overall health but may never require treatment beyond active surveillance. Conversely, men with aggressive prostate cancer in this age group should not be denied the opportunity for the diagnosis and treatment which could affect their

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length and quality of life. Once the concept of diagnosis automatically prompting treatment is dispelled, the issue of prostate cancer screening in any age group becomes less controversial. For a review on estimating treatment benefits for the elderly, see Welch et al, 1996.[187]

The Use of PSA Testing for Pretreatment Staging of Prostate Cancer

Routine radiographic staging, such as with bone scan, computed tomography (CT), or magnetic resonance imaging (MRI), or surgical staging with pelvic lymph node dissection is not necessary in all cases of newly diagnosed prostate cancer (Figure 2).[188, 189] Clinical criteria can identify patients for whom such staging studies are appropriate.

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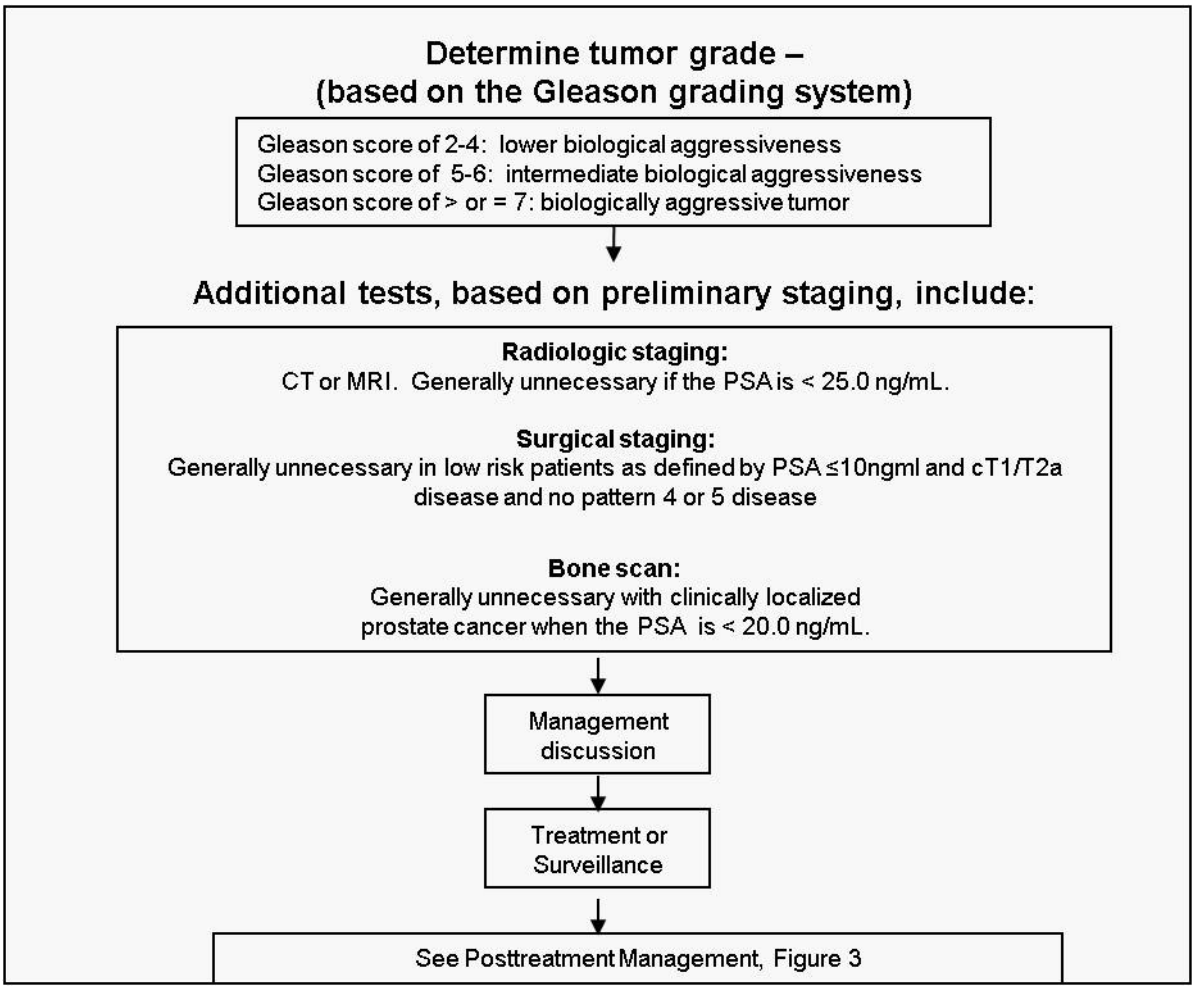

Figure 2: Staging – Once Prostate Cancer is Diagnosed

1. Pretreatment serum PSA predicts the response of prostate cancer to local therapy.

Accurate pretreatment staging is crucial in prostate cancer management. Serum PSA levels correlate with the risk of extra-prostatic extension, seminal vesicle invasion, and lymph node involvement. Patients with serum PSA levels of less than 10.0 ng/mL are most likely to respond to local therapy.

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Pretreatment serum PSA is an independent predictor of response to all forms of therapy. Nomograms incorporating pretreatment PSA are statistical models that use important variables to calculate the probability of clinical endpoints, and have been useful in predicting outcomes of prostate cancer treatment.[15, 16]

Pretreatment PSAV is an independent predictor of prostate cancer-specific and overall mortality following therapy. For example, men with localized prostate cancer and a pretreatment PSAV greater than 2.0 ng/mL/year may experience a significantly higher risk of cancer recurrence and prostate cancer-specific mortality following surgery or external beam radiotherapy.[39, 40]

2. Routine use of a bone scan is not required for staging asymptomatic men with clinically localized prostate cancer when their PSA level is equal to or less than 20.0 ng/mL.

An analysis of 23 studies examining the utility of bone scan found metastases in 2.3% of men with PSA levels <10.0 ng/mL, 5.3% in men with PSA levels from 10.1 to 19.9 ng/mL, and 16.2% in men with PSA levels >20.0 ng/mL.[190] The authors concluded that low-risk patients are unlikely to have disease identified by bone scan. Accordingly, bone scans are generally not necessary in patients with newly diagnosed prostate cancer who have a PSA <20.0 ng/mL unless the history or clinical examination suggests bony involvement. As metastatic disease is significantly more common in advanced local disease or in high-grade disease, and as some high-grade prostate cancers have lower PSA values, it is reasonable to consider bone scans at the time of diagnosis when the patient has Gleason 8 or greater disease, or stage ≥T3 prostate cancer, even if the PSA is <10.0 ng/mL.[190, 191]

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3. Computed tomography or magnetic resonance imaging scans may be considered for the staging of men with high-risk clinically localized prostate cancer when the PSA is greater than 20.0 ng/mL or when locally advanced or when the Gleason score is greater than or equal to 8.

Although this guideline is commonly used by the experts in the field, supporting data are lacking. CT scan is not a useful staging procedure for the vast majority of patients with newly diagnosed prostate cancer for whom the estimated incidence of positive lymph nodes is approximately 5%.[192-194] CT is rarely positive when the PSA is <20.0 ng/mL and is generally reserved for men whose risk of lymph node metastasis is ≥20% by Partin table estimation.[195] Additionally, several studies have found a correlation between Gleason score and lymphadenopathy detected on imaging; 1.2% of patients with Gleason score ≤7 have detectable lymph node enlargement on CT scan, compared to 12.5% in men with Gleason score ≥8 .[190] However, it should be noted that many men with Gleason scores of 8-10 on biopsy, may be downgraded based on examination of radical prostatectomy specimens.[196] CT scan identification of pelvic adenopathy depends upon lymph node enlargement, and the correlation between nodal size and metastatic involvement is poor.[197] Although the histologic incidence of positive pelvic lymph nodes is substantial when PSA levels exceed 25.0 ng/mL, the sensitivity of CT scanning for detecting positive nodes is only about 30% to 35%, even at these levels.[193]

For similar reasons, MRI scanning using a body coil is also not a useful staging procedure in the vast majority of patients with newly diagnosed prostate cancer, because sensitivity is again determined by lymph node size.[198] Its sensitivity for detecting nodal metastases, as determined from the analysis of seven studies using MRI, was only 36%.[194] Endorectal coil MRI together with magnetic resonance spectroscopy (MRS) for characterization of cancer stage and volume is

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still considered an investigational procedure, but has shown promise in preliminary studies.[199, 200] MRS allows MRI technology to identify functional and metabolic abnormality.[201] However, imaging modalities of various types are being refined and will likely play a greater role in the routine diagnosis, staging, treatment and post-treatment evaluation of prostate cancer in the future.[202, 203]

4. Pelvic lymph node dissection for clinically localized prostate cancer may not be necessary if the PSA is less than 10.0 ng/mL and the Gleason score is less than or equal to 6.

Although pelvic lymph node dissection is often routinely performed in conjunction with radical prostatectomy, its morbidity, even if limited, must be considered. This is especially true in cases where it offers little additional information. A benefit to standard lymph node dissection has not been conclusively shown.[205] Several studies have shown increased sensitivity; in addition, that there may be a recurrence and survival benefit associated with *extended* lymph node dissection, especially in intermediate- to high-risk patients, even when all nodes are negative.[205-208] In extended lymphadenectomy, the area of additional dissection involves the region from the external iliac vein to the internal iliac vein medially, and to the bifurcation of the common iliac artery superiorly, rather than to just the obturator fossa.[160] The benefit accruing to this more extended dissection must be balanced against the potential for increased morbidity, however, making careful patient selection critical.[209]

Measurement of pretreatment PSA level, supplemented with clinical stage and Gleason score information, can identify a subset of patients in whom the incidence of nodal metastases is very low (3% to 5%). Patients with a pretreatment PSA level <10.0 ng/mL and a Gleason score ≤6

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rarely have nodal metastases, and it may be appropriate to omit lymphadenectomy in this group. These observations have been made in several large series of patients.[56, 210-213]

The Use of PSA in the Post-treatment Management of Prostate Cancer

1. Periodic PSA determinations should be offered to detect disease recurrence.

The early biochemical (PSA) detection of recurrence after definitive local therapy (Figure 3) may prompt further treatment. The optimal strategy for such adjunctive therapy, including time of initiation, remains uncertain, and it is the focus of ongoing clinical trials and study. Different definitions of biochemical recurrence exist after surgery and radiation, making it difficult to compare recurrence free survival by time period.[214] To date, it is unknown whether survival is altered by using PSA values to time the initiation of salvage therapy.[215, 216] Treatment options for recurrence following radical prostatectomy include surveillance, salvage radiation therapy, other forms of focal therapy, androgen deprivation and enrollment in clinical trials evaluating new therapies. Treatment options for recurrence after radiation therapy include surveillance, androgen deprivation, cryotherapy, additional radiation (i.e. brachytherapy), and salvage radical prostatectomy. Salvage therapies in both instances may be more effective if initiated early, but the overall impact of any form of salvage therapy is currently the subject of much study. [217, 218]

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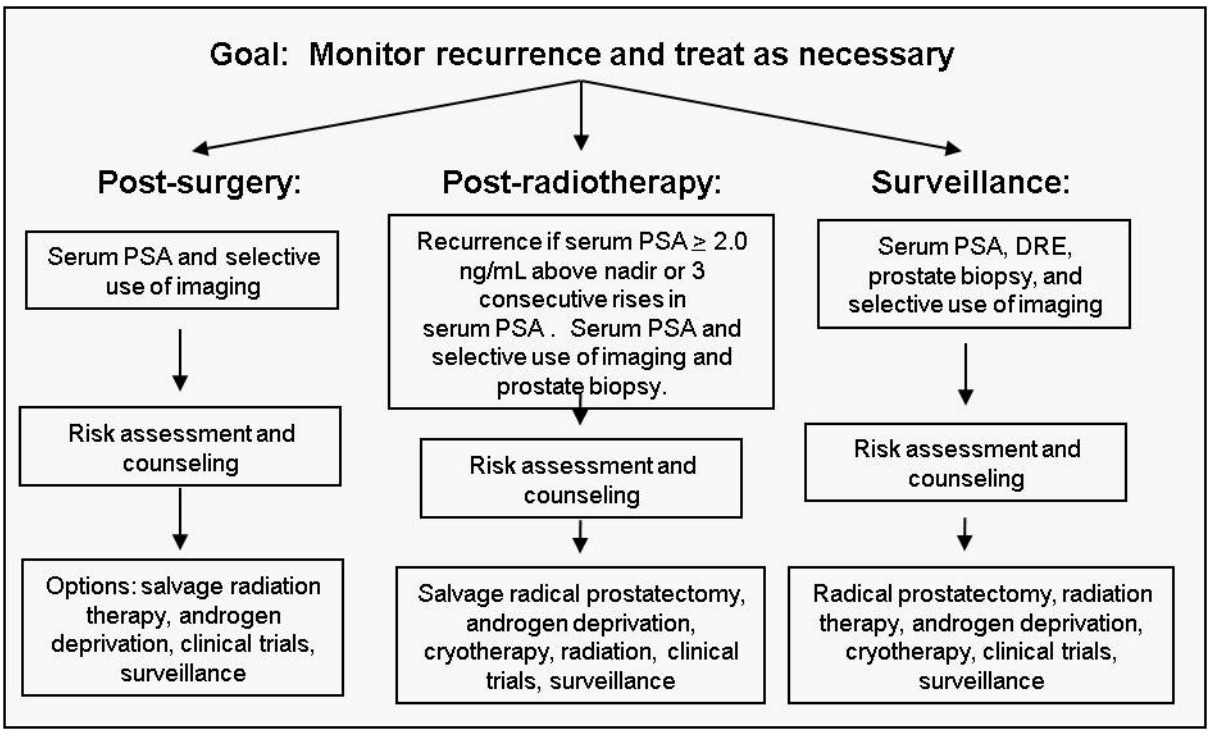

Figure 3: Posttreatment Assessment and Management

2. Serum PSA should decrease and remain at undetectable levels after radical prostatectomy.

A detectable PSA following radical prostatectomy is associated with eventual clinical disease recurrence in some, but not all patients. It may also be due to the presence of benign glands.[219] The AUA defines biochemical recurrence as an initial PSA value ≥0.2 ng/mL followed by a subsequent confirmatory PSA value ≥0.2 ng/mL.[220] However, a cut-point of 0.4 ng/mL may better predict the risk of metastatic relapse.[221] This cut-point was selected as a means of reporting outcomes, however, rather than as a threshold for initiation of treatment. The median interval from PSA recurrence to cancer death is between 5 and 12 years, depending upon the Gleason score and PSA doubling time. The utility of "ultrasensitive" PSA testing has not been established as yet. Although its use seems to distinguish between those who are less likely and

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those who are more likely to recur, there may be considerable variability and inconsistency of results at low PSA levels.[222, 223]

3. Serum PSA should fall to a low level following radiation therapy, high intensity focused ultrasound and cryotherapy and should not rise on successive occasions.

Following radiation therapy, the PSA value should fall to a low level and then remain stable. PSA values <0.2 are uncommon after external beam radiotherapy, which does not ablate all prostate tissue. A consistently rising PSA level usually, though not always, indicates cancer recurrence. The number of rises needed to define a failure has been a matter of debate, but a consensus is emerging in support of the American Society for Therapeutic Radiation and Oncology (ASTRO) definition of failure: three successive rises above nadir.[224] More recently it has been recognized that this endpoint is relevant only for external beam radiotherapy and even then it is easily confounded by biological variability.

The change in PSA following interstitial prostate brachytherapy is complex. Over the first year, the PSA level declines, then rises again in the second or third year in up to 40% of cases, only to fall back to much lower values by year four.[225-227] Although these rises (or "benign bounces") are generally small (<0.8 ng/mL), they can, on occasion, be as high as 10.0 ng/mL, and they may last for 6 to 18 months. Their cause is uncertain, but they may correspond to infarction of the prostate occurring as a late vascular effect of the radiation. The principal concern regarding the benign bounce is that it may be confused with failure and lead to the initiation of unnecessary additional therapy. Ironically, bounces may actually predict a particularly good ultimate outcome.[228] By the fifth year after interstitial prostate brachytherapy, the PSA level is <0.6

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ng/mL in 90% of patients who are clinically disease free. The median PSA level of these patients is <0.1 ng/mL.[229]

A Consensus Committee was convened in Phoenix in 2005 to reconcile these differences and to produce a universal definition of PSA failure after all forms of radiation therapy, with or without androgen deprivation. The Committee arrived at the following conclusions: that any rise in PSA level of 2.0 ng/mL or more, over and above the nadir, predicted true failure with great sensitivity and specificity after both external beam radiotherapy and interstitial prostate brachytherapy, irrespective of whether either of these treatments was accompanied by androgen deprivation. The Consensus Committee also determined that the time of failure should not be backdated to the first rise in PSA.[230, 231] This endpoint, the "Phoenix Definition," was designed to make comparison between any radiation series possible but did not facilitate easy comparisons with surgical series.[232, 233] It was designed as a research tool, rather than as a trigger for a clinical intervention. The Consensus Committee further noted that setting a "target PSA" was not possible after external beam radiotherapy, although for interstitial prostate brachytherapy a PSA level of <0.7 ng/mL at five years would be reasonable. They also commented that the PSA level continues to decline more than five years after interstitial prostate brachytherapy, allowing for even tighter definitions of failure with enough follow-up.

Less data exist to document PSA behavior after either cryotherapy or high-intensity focused ultrasound.

4. PSA nadir after androgen suppression therapy predicts mortality

Though it has long been known that achievement of a low PSA nadir after hormonal therapy has prognostic significance,[233 234] there are now increasing data that quantitatively link this end point

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to survival. For patients with metastatic disease receiving androgen suppression therapy, failure to achieve a PSA nadir of <4.0 ng/mL seven months after initiation of therapy is associated with a very poor prognosis (median survival: approximately one year) whereas those patients with a PSA nadir of <0.2 ng/mL have a relatively good prognosis (median survival: over six years). For patients with PSA nadirs >0.2 and <4.0 ng/mL, the prognosis is intermediate (median survival of 44 months).[235]

Additional data to support the importance of PSA nadir following hormonal therapy are derived from studies of patients with nonmetastatic disease. For patients with a PSA rise following radical prostatectomy or radiation and no radiologic evidence of metastases, a PSA nadir of >0.2 ng/mL within eight months of androgen suppression is associated with a 20-fold greater risk of prostate cancer-specific mortality as compared to those patients with a PSA nadir of <0.2 ng/mL.[236] A PSA nadir of >0.2 ng/mL in the setting of a PSADT of <3 months is an ominous finding. Taken together, these data clearly support the prognostic importance of the value of the PSA nadir after androgen deprivation therapy and suggest that careful PSA monitoring after the initiation of such therapy can effectively identify those patients with a poor prognosis.

For patients with hormone-refractory disease (defined as disease progression despite castrate levels of testosterone), the relationship between PSA decline and prognosis remains controversial. Despite multiple studies indicating that PSA declines of >50% correlate with survival,[237-239] large well-controlled studies have shown mixed results.[240-242] Attempts to establish PSA declines as a surrogate end-point for patients in this setting have not been universally accepted and more investigation is necessary to create consensus. However, PSA kinetics do appear to correlate with outcomes in this group of patients.[243]

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5. Bone scans are indicated for the detection of metastases following initial treatment for localized disease but the PSA level that should prompt a bone scan is uncertain. Additional important prognostic information can be obtained by evaluation of PSA kinetics.

For patients with a rising PSA level after surgery or radiation for localized prostate cancer, the estimate of total PSA alone is an imperfect predictor of a positive bone scan. In studies where bone scans have been positive in this setting, PSA values have averaged between 30.0 and 140.0 ng/mL.[244-247] For this reason, the lowest PSA value at which bone scans will always be positive is uncertain. Several analyses[247,248] indicate that the rate of PSA change is an additional critical variable in this setting. For men with a PSA doubling time >6 months and a serum PSA <10.0 ng/mL, the probability of a positive scan is extremely low (less than 1%); however for patients with a PSADT of <6 months, there is approximately a 10% chance of a positive bone scan. Nomograms have been constructed which predict the likelihood of a positive bone scan using a combination of PSA kinetics and PSA values.[248] Thus, the use of routine bone scans in the setting of a PSA rise following local therapy is not justified, particularly for those with a PSADT of >6 months and a PSA value of <10.0 ng/mL.

6. The kinetics of PSA rise after local therapy for prostate cancer can help distinguish between local and distant recurrence.

Distinguishing local from distant recurrence is problematic after local treatments as most patients with a PSA rise have a negative physical exam and noninformative imaging tests. A positive biopsy in the prostate (postradiation) or at the anastomotic site (postradical prostatectomy) may not be the only reason for the rise in PSA, as a distant recurrence may also be a contributing

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factor. Accordingly, other variables are necessary for assessment. Perhaps the best method to assess for local recurrence after radical prostatectomy is to review the prognostic variables associated with durable responses to salvage radiation therapy. Pooled data from multiple centers indicate several variables in the salvage radiation setting that are predictive of a durable response to salvage radiation.[249] These variables include pathology findings at the time of surgery (seminal vesicle or margin positivity), PSA doubling time, PSA level at the beginning of radiation, and Gleason score. The PSA recurrence-free interval and the pre-operative PSA level are not thought to be consequential in predicting durable responses to radiation in this setting. Using these variables, one can risk-stratify patients into those more and less likely to respond to radiation. Of note, a positive post radical prostatectomy anastomotic biopsy does not independently predict positive responses to salvage radiation, thus calling into question the value of this procedure.[250]

Even patients with multiple adverse risk factors may respond to salvage radiation, especially those with positive surgical margins receiving treatment when the PSA is low (i.e. 0.5 to 1.5 ng/mL) and slowly rising.[251] Given that salvage radiation is the only potentially curative treatment in this setting, such patients should strongly consider radiation.[252] Whether or not radiation administered with concomitant androgen suppression is superior to radiation alone is an unsettled issue.

Predictors of favorable response to postradiation salvage prostatectomy are less well defined compared with those for salvage radiation following radical prostatectomy. Recurrent disease noted on prostate biopsy, PSA less than 10.0 ng/mL (preferably PSA less than 5.0 ng/mL), a

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clinically localized cancer (ie T1C or T2), and no evidence of metastases on prior evaluation or pre-operative imaging are reasonable criteria for consideration.[253, 254]

Excellent data now indicate that patients with a long PSADT (>15 months) have a low likelihood of prostate cancer-specific mortality over a 10 year period,[255] and active surveillance may be considered for those with a life expectancy of <10 years. In contrast, patients with a PSADT <3 months have a median overall survival of 6 years following PSA failure, and are likely have distant disease.[255, 256] In addition, patients experiencing a relapse after local therapy may be candidates for clinical trials.

Methods Used in Best Practice Statement Development

The AUA convened a multidisciplinary panel for the purpose of developing a resource about PSA testing for urologists and primary care physicians. Panel membership included six urologists, one radiation oncologist, two medical oncologists, one internist and one epidemiologist. Funding in support of panel activities was provided by the AUA. Panel members received no remuneration for their efforts, and each member provided conflict of interest disclosure.

The Panel formulated its policy statements and recommendations by consensus, based on a review of the literature and the Panel members' own expert opinions. The current policy was based on a reassessment of the previous policy published in 2000. After Panel members agreed on the general areas to be covered, each member took on the task of conceptualizing and writing and/or revising a section of the document in an area where he/she had specific expertise. Every part of the document was thoroughly critiqued by Panel members, both in written comments and in verbal discussions in a series of conference calls. Over the course of successive manuscript

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revisions, the Panel scrutinized and modified the conceptual framework, reworked the wording of key statements, and reexamined supporting evidence reported in the literature until Panel members reached consensus.

The Panel did not use any particular methodology to develop its consensus statements. As noted above, these statements are based upon Panel members' expert opinions and knowledge of the published literature, and are referenced with what the Panel considered to be the most appropriate publications. The Panel also did not address issues of costs or cost-effectiveness in this document, nor did it systematically incorporate patient values and preferences in the analysis. However, the Panel did include ample information in the document to assist patients as well as health care professionals in decision-making regarding the best use of serum PSA for prostate cancer early diagnosis, staging, and treatment follow-up of prostate cancer.

After the Panel reached an initial consensus, 70 peer reviewers representing the following medical specialties reviewed the manuscript: family practice, internal medicine, radiology, oncology and urology. The panel made numerous document changes based on insight from peer reviewers, Thereafter, the document was submitted for approval to the Practice Guidelines Committee of the AUA and then to the AUA Board of Directors for final approval.

The panel recognizes the limitations of the document and acknowledges that recommendations are likely to change with new information. However, it is hoped the information contained will assist physicians, other healthcare providers and patients in using serum PSA efficiently and responsibly.

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Conflict of Interest Disclosures

All panel members completed Conflict of Interest disclosures. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

Consultant or Advisor: Peter Albertsen, Blue Cross/Blue Shield (C), GlaxoSmithKline (C); Richard J. Babaian, Endocare (C); **Investigator:** Peter Carroll, National Cancer Institute (C); Peter Albertsen, National Cancer Inst. (C), Agency Health Care Quality (C), Aureon Corporation (C), Sanofi (C), Ikonysis (C); Oliver Sartor, AstraZeneca (U), Sanofi-Aventis (C), GlaxoSmithKline (C); **Meeting Participant or Lecturer:** Peter Carroll, Astra Zeneca (C), Takeda (C); Anthony Zietman, Ismar Medical (C), Ismar Healthcare (C); Kirsten Greene, Takeda (C); **Other: Advisor and Investigator:** Richard J. Babaian, Gen-Probe (C); Other: **Scientific Advisory Board:** Deborah Ann Kuban, Calypso Medical (C).

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Acknowledgements and Disclaimers: Prostate – Specific Antigen Best Practice Statement

The supporting literature review and the drafting of this document were conducted by the Prostate-Specific Antigen Best Practice Statement Update Panel created in 2006 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel chair who in turn appointed the Panel members, urologists and other physicians with specific expertise regarding the prostate. The mission of the Panel was to develop recommendations to support optimal clinical practices in the use of PSA. This document was submitted to 70 urologists and other health care professionals for peer review. After revision of the document based upon the peer review comments, the best practice statement was submitted to and approved by the PGC and the Board of Directors of the AUA. Funding of the Panel and of the PGC was provided by the AUA, although Panel members received no remuneration for their work. Each member of the PGC and of the Panel furnished a current conflict of interest disclosure to the AUA. All disclosures were reviewed by the panel Chair, acknowledged in the document and made available to AUA Board of Directors.

The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the use of PSA in screening for prostate cancer. The report is based on a review of available professional literature, as well as on clinical experience and expert opinion.

This document provides guidance only, and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, the practice or

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protocol may change. Today the best practice statements represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, this document does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs and preferences. Conformance with the practices in this document cannot guarantee a successful outcome.

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Appendix 1: Members of the Prostate-Specific Antigen Best Practice Policy Panel (2000)

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