

# Prostate Specific Antigen Best Practice Statement: 2009 Update

## Abbreviations and Acronyms

AUA = American Urological Association

BPH = benign prostatic hyperplasia

CT = computerized tomography

DRE = digital rectal examination

ERSPC = European Randomized Study of Screening for Prostate Cancer

MRI = magnetic resonance imaging

NCI = National Cancer Institute

PCPT = Prostate Cancer Prevention Trial

PLCO = The Prostate, Lung, Colon, and Ovary Trial

PSA = prostate specific antigen

PSADT = PSA doubling time

PSAV = PSA velocity

TZPSAD = transition zone PSA density

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**Purpose:** We provide current information on the use of PSA testing for the evaluation of men at risk for prostate cancer, and the risks and benefits of early detection.

**Materials and Methods:** The report is a summary of the American Urological Association PSA Best Practice Policy 2009. The summary statement is based on a review of the current professional literature, clinical experience and the expert opinions of a multispecialty panel. 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.

**Results:** There are two 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 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.

**Conclusions:** Although recently published trials show different results regarding the impact of prostate cancer screening on mortality, both suggest that prostate cancer screening leads to overdiagnosis and overtreatment of some patients. Therefore, men should 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 diagnosed with prostate cancer.

**Key Words:** prostatic neoplasms, prostate-specific antigen, mass screening, neoplasm staging, treatment outcome

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.

## THE USE OF PSA FOR EARLY DETECTION OF PROSTATE CANCER

PSA testing is one measure that can be used for characterization and risk assessment of prostate cancer prior to therapy, as well as for development of treatment recommendations (fig. 1). Other measures include Gleason score, clinical stage, biopsy tumor volume

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Requests for reprints: Guidelines Department, American Urological Association, 1000 Corporate Blvd., Linthicum, Maryland 21090.

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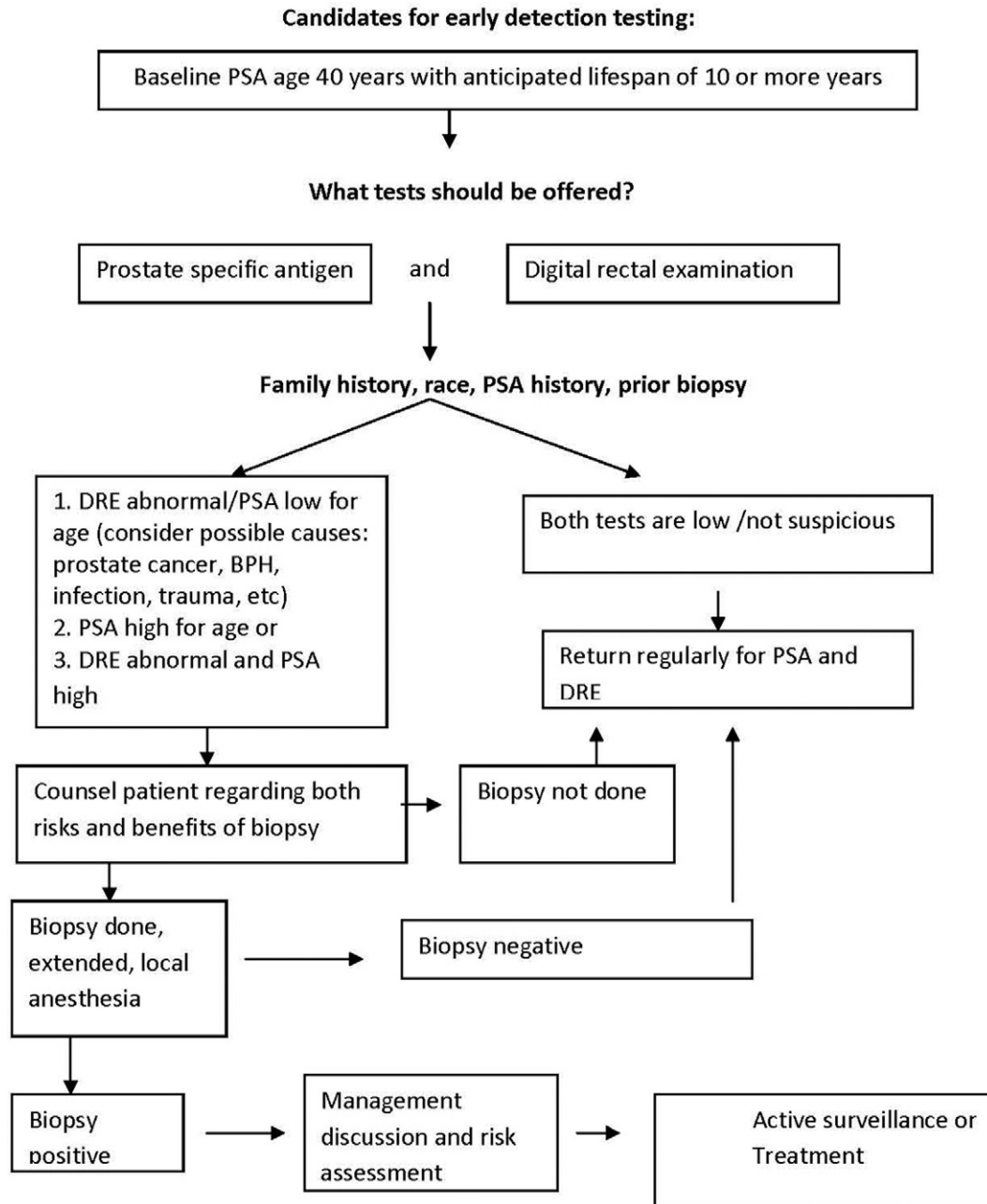
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**Figure 1.** Early detection

(number and percent of cancer in positive cores), and imaging. The use of PSA testing for the early detection of prostate cancer remains controversial, however, due to strong evidence for overdiagnosis and overtreatment.<sup>1</sup>

There has been a gradual but steady decline in prostate cancer mortality in the U.S. of approximately 30%.<sup>2</sup> This trend began fairly soon after the introduction of PSA testing, and there is evidence from statistical modeling studies that PSA screening has played a role.<sup>3</sup> Screening with PSA is responsible for the diagnosis of prostate cancer at ear-

lier stages where active treatment may reduce prostate cancer specific mortality.<sup>4-6</sup> The European Randomized Study of Screening for Prostate Cancer demonstrated a 20 percent relative reduction in prostate cancer deaths among those screened when compared to those that were not at 9 years.<sup>1</sup> The Prostate, Lung, Colon, and Ovary Trial of the National Cancer Institute found no difference in prostate cancer deaths at 7–10 years of follow-up when comparing those screened to those that were not.<sup>7</sup> The results of this study should be reviewed with some caution due to pre-screening of the study pop-

ulation with PSA and the high percentage of men who underwent PSA screening in the control group. 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; therefore it is still not clear that prostate cancer screening results in more benefit than harm. 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.

Because there is now evidence from a well conducted, randomized, controlled trial regarding a mortality decrease associated with PSA screening, the AUA is recommending PSA screening for well-informed men with an estimated ten year life expectancy who wish to pursue early diagnosis. The risks of overdiagnosis and overtreatment should be discussed. In addition, all discussions of treatment options should include active surveillance as a consideration, since many men with screen-detected prostate cancers may not need immediate treatment.

## EARLY DETECTION

### 1. The Goal of Early Prostate Cancer Detection

The goal of early detection is to reduce the morbidity and mortality of prostate cancer. Studies have shown that long-term survival is considerably diminished in men diagnosed with prostate cancer that has already spread to regional lymph nodes or 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.<sup>8</sup>

### 2. Determination of Clinically Significant Prostate Cancer

There is currently no universally accepted definition of clinically significant or insignificant prostate cancer. Previous studies have focused on measures such as cancer volume, stage, and histologic grade.<sup>9</sup> The number of biopsies showing cancer, as well as the extent of cancer in individual cores, may be helpful in assessing the likelihood of insignificant disease.<sup>10</sup> Tumor grade appears to be the strongest prognostic factor although this is subject to sampling errors.<sup>10</sup> Although not well validated, many have defined tumor volume exceeding 0.5 ml to be clinically significant. Tumors volumes of 0.5 to 1.9 ml are often associated with higher PSA values and are more likely to progress or spread beyond the prostate (extraprostatic disease). Epstein et al. suggested 4 criteria predictive of insignificant cancer: tumor volume < 0.5 cm<sup>3</sup>, 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.<sup>9</sup> However, a recent European study found that these criteria can underestimate the aggressiveness of the tumor in up to 24% of cases.<sup>11</sup> No currently available noninvasive imaging method can consistently and reliably measure tumor volume. Risk assessment tools (i.e. nomograms, probability tables, etc) can be used to help determine the likelihood of pathologic outcomes and recurrence free survival after treatment.<sup>12</sup>

### 3. Men Who Wish to be Screened for Prostate Cancer Should Have Both a PSA Test and a DRE

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. However, data from the ERSPC found that DRE did not improve prostate cancer screening over PSA testing alone.<sup>13</sup>

### 4. A Variety of Factors Can Affect PSA Levels and Should be Considered in the Interpretation of Results

Prostatitis, benign prostatic hyperplasia, urethral or prostatic trauma, and prostate cancer can all be associated with elevated serum PSA levels. Surgical or medical castration (with LHRH-agonist or antiandrogen therapy) will lower PSA levels dramatically. Finasteride and dutasteride will lower PSA levels by approximately 50% regardless of the dose.<sup>35</sup> Ejaculation and DRE have been reported to increase PSA levels but studies have shown the effects to be variable or insignificant. Prostate biopsy will usually cause substantial elevation of PSA levels and PSA testing should be postponed for at least three to six weeks. Hemodialysis and peritoneal dialysis have not been found to alter total serum PSA levels but free PSA is altered and should not be used.<sup>14</sup>

Importantly, 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. It is necessary to use the same assay for longitudinal monitoring because PSA assays are not interchangeable and there is no acknowledged conversion factor between them.<sup>15,16</sup> Consideration should be given to confirming an abnormal PSA before proceeding to biopsy.

### 5. Methods to Improve PSA Sensitivity and Specificity

PSA testing in patients with a serum PSA level above 4.0 ng/ml has a sensitivity of about 20% in contemporary series.<sup>17</sup> The specificity of PSA testing is approximately 60% to 70% at this cutoff. One way to improve sensitivity of PSA is to use a lower

threshold value for all men. This improves the likelihood of detecting cancers, including 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 decrease 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.<sup>18</sup>

Assessment of PSA kinetics, PSADT or 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.<sup>19</sup> 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.<sup>12,20,21</sup> 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 proposed.<sup>20</sup> 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.<sup>16,22</sup> To correctly measure PSAV, use of at least three PSA values over a time period of at least 18 months is recommended.<sup>12,21</sup>

Because serum PSA tends to increase with age, the use of higher “normal” levels for older men results in fewer biopsies but may also increase the risk of missing high grade cancers in older men, and overdetect smaller volume/lower grade tumors in younger men.<sup>23</sup> 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, 0.9 ng/ml for men in their 50s, 1.2 for men in their 60s, and 1.5 for men in their 70s.<sup>24</sup>

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. 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. 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.<sup>25</sup>

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, or the size of the transition zone of the prostate (PSA density = PSA/gland volume) can reduce the number of biopsies performed.<sup>26</sup> 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 methods—age-adjusted PSA, free/total PSA ratio 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 such as nomograms and risk calculators, incorporating multiple variables, can also be used to determine the need for biopsy. 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. However, using a combination of factors, as described above, improves specificity and, importantly, may better detect higher risk cancers compared to using single PSA cut points and DRE alone.

## 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 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). 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

**Table 1.** Age-specific reference ranges for serum PSA

Age Range	Reference 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

**Table 2.** A continuum of prostate cancer risk exists even at traditionally low prostate-specific antigen (PSA) values<sup>70</sup>

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.

level is 4.0 to 10.0 ng/ml; and 43% to 65% if the PSA level is above 10.0 ng/ml.<sup>25,27</sup> 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 cut-point in combination with DRE alone can lead to an overestimation of risk in some and underestimation in others. 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.

Prostate tissue for diagnosis of prostate cancer can be obtained transrectally, transurethraly, and via a perineal approach. The most common method is transrectal, ultrasound-guided prostate biopsy, which is usually performed as an outpatient procedure with local anesthesia. A standard biopsy scheme consists of at least 8 to 12 cores of tissue targeting the peripheral zone at the apex, mid gland, 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. Extended 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%. 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. Occasionally, prostate cancer may be detected when tissue is removed from

the central portion of the prostate, usually during surgery for BPH.

### 7. Early Detection and Risk Assessment of Prostate Cancer Should be Offered to Healthy, Well-Informed Men 40 Years of Age or Older

Previously, the AUA recommended that early detection begin at age 50 years for men at average risk of prostate cancer, and sooner for those men at higher lifetime risk (positive family history in a first-degree relative, African American race). This age has been lowered. 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.<sup>28</sup> One way to identify this higher-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 higher risk for prostate cancer.<sup>28</sup>

The rationale for decreasing the age of testing to 40 years takes into account the following data. 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.<sup>29</sup> 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. Given the relationship between PSAV and death from prostate cancer decades later,<sup>50</sup> 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. Finally, those men found to be at increased risk of prostate cancer, but who do not have it, may be offered chemoprevention.<sup>30,31</sup>

The recommendation to perform PSA testing annually among men who decide to be tested is also not evidence-based but there is strong evidence that re-screening intervals should be based on the results of the initial PSA test.<sup>28,32</sup>

Because of the long natural history of most prostate cancers and competing causes of death,<sup>32</sup> the benefits of screening may decline rapidly with age.<sup>33</sup> 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.<sup>34</sup> 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. Addition-

ally, 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 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 length and quality of life.

**THE USE OF PSA TESTING FOR PRETREATMENT RISK: ASSESSMENT OF PROSTATE CANCER**

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.<sup>35,36</sup> Routine radiographic staging, such as with bone scan, CT or MRI, or surgical staging

with pelvic lymph node dissection is not necessary in all cases of newly diagnosed prostate cancer (fig. 2).<sup>37</sup> Clinical criteria can identify patients for whom such staging studies are appropriate.

**1. Use of PSA in Risk Stratification and Prognosis**

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. In addition, the 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.

Furthermore, 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.<sup>38</sup> Biochemical recur-

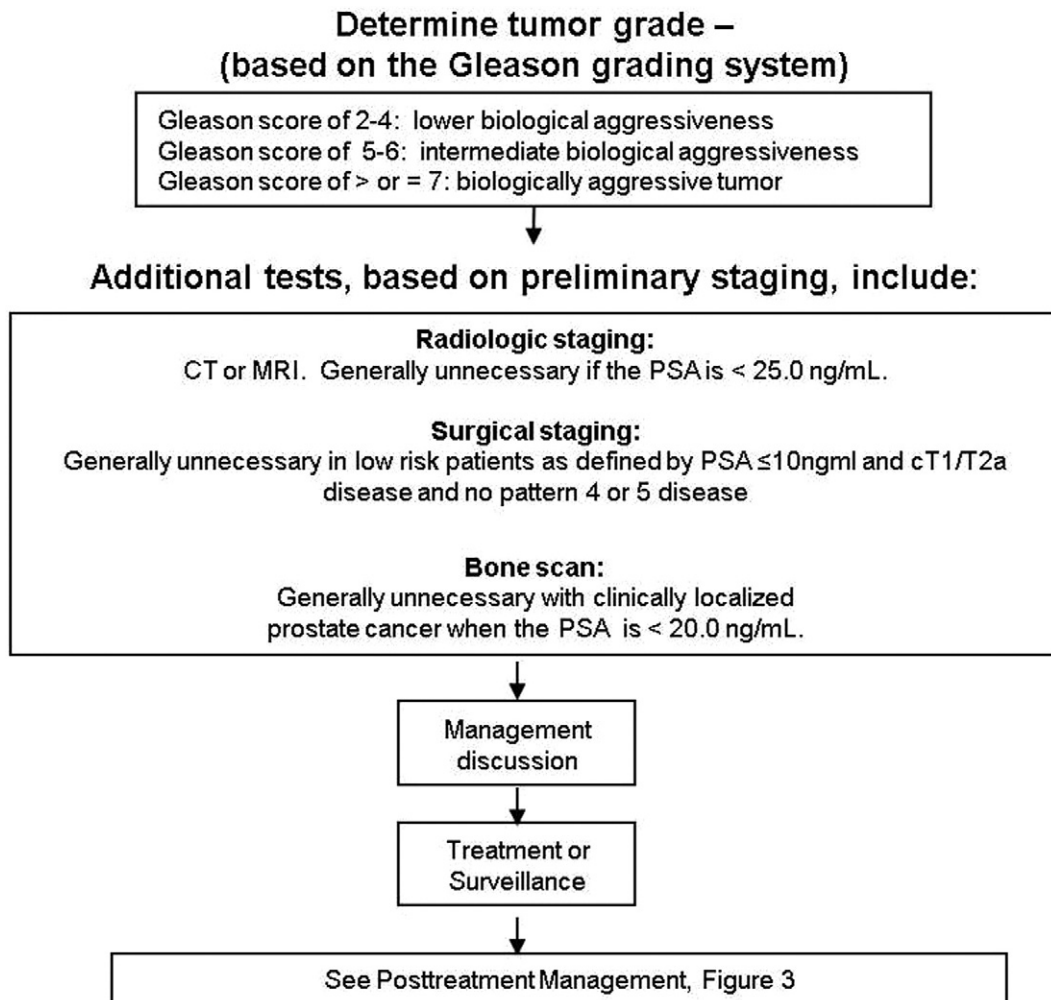


Figure 2. Staging after prostate cancer is diagnosed

rence 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.<sup>36,38</sup> 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. 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.

The PSAV prior to treatment of prostate cancer is also associated with the risk of prostate cancer death after treatment.<sup>12,21</sup> 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 approximate 10-fold greater risk of death from prostate cancer in the decade after radical prostatectomy.<sup>12</sup>

## 2. Radiographic Imaging

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. Metastatic disease is significantly more common in advanced local disease or in high-grade disease, and it is reasonable to consider bone scans when the patient has Gleason 8 or greater disease, or stage  $\geq$ T3 prostate cancer, even if the PSA is <10.0 ng/ml.<sup>2,39</sup> CT or MRI 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 identification of pelvic adenopathy depends upon lymph node enlargement, and the correlation between nodal size and metastatic involvement is poor.

## 3. 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

Lymphadenectomy is not needed in low risk patients. Patients with higher risk disease may benefit from this procedure. 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.<sup>40</sup> The benefit accruing to this more extended dissection must be balanced against the potential for increased morbidity, however, making careful patient selection critical.

## THE USE OF PSA IN THE POSTTREATMENT MANAGEMENT OF PROSTATE CANCER

### 1. Periodic PSA Determinations Should be Offered to Detect Disease Recurrence

Treatment options for recurrence following radical prostatectomy include surveillance, salvage radiation therapy, other forms of focal therapy, systemic therapy (i.e. androgen deprivation, chemotherapy) and enrollment in clinical trials evaluating new therapies (fig. 3). 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.<sup>41</sup>

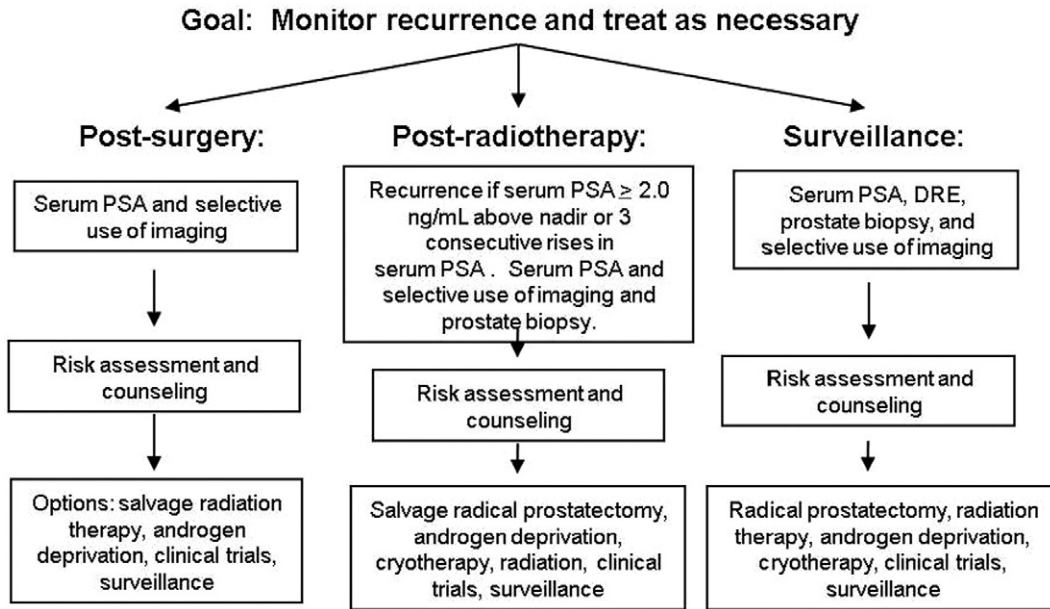
### 2. PSA After Radical Prostatectomy

A detectable PSA following radical prostatectomy is associated with eventual clinical disease recurrence in some patients. It may also be due to the presence of benign glands. The AUA defines biochemical recurrence as an initial PSA value  $\geq$ 0.2 ng/ml followed by a subsequent confirmatory PSA value  $\geq$ 0.2 ng/ml.<sup>42</sup> However, a cut-point of 0.4 ng/ml followed by another increase may better predict the risk of metastatic relapse.<sup>43</sup> This cut-point was selected as a means of reporting outcomes, however, rather than as a threshold for initiation of treatment.

### 3. PSA After Radiation Therapy

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. The change in PSA following interstitial prostate brachytherapy is complex and is characterized by intermittent rises called "benign bounces." The median PSA level of these patients is <0.1 ng/ml.<sup>44</sup>

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. A Consensus Committee was convened in Phoenix in 2005 and arrived at the following conclusions: that any rise in PSA level of 2.0 ng/ml or more, over and above the nadir, predicted failure after both external beam radiotherapy and interstitial prostate brachytherapy, irrespective of androgen deprivation. The Consensus Committee also determined that the time of failure should not be backdated to the first rise in PSA.<sup>45</sup> Although a "target PSA" was not possible after external beam radiotherapy, a PSA level of <0.7 ng/ml at five years



**Figure 3.** Posttreatment assessment and management

is reasonable for brachytherapy. PSA levels continue to decline more than five years after interstitial prostate brachytherapy.

#### 4. PSA Nadir After Androgen Suppression

PSA kinetics do appear to correlate with outcomes in this group of patients.<sup>46</sup> In 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 median survival of approximately one year whereas patients with a PSA nadir of <0.2 ng/ml have a median survival of over six years. 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 patients with a PSA nadir of <0.2 ng/ml.<sup>47</sup> 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.

#### 5. PSA Kinetics and Salvage Therapy

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. When the PSA is low (i.e. 0.5 to 1.5 ng/ml) even patients with

multiple adverse risk factors may respond to salvage radiation after prostatectomy, especially those with positive surgical margins. Given that salvage radiation is the only potentially curative treatment in this setting, such patients should strongly consider radiation.<sup>48</sup>

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 clinically localized cancer (i.e. T1C or T2), and no evidence of metastases on prior evaluation or preoperative imaging are reasonable criteria for consideration.<sup>49</sup>

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,<sup>50</sup> 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.<sup>50,51</sup> In addition, patients experiencing a relapse after local therapy may be candidates for clinical trials.

#### SUMMARY

Assessment of serum PSA plays important roles in the detection and assessment of prostate cancer. The updated guidelines reflect information to date. It is recognized that they will need to be

revised in a timely fashion based on new information, which is likely to accrue rapidly. It is also clear that new serum, tissue and germline mark-

ers will be developed which will complement or may even replace serum PSA for the applications reviewed in this update.

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