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Understanding total PSA cutoff values

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Abstract

PSA is an important part of the early detection strategy for prostate cancer. Currently there are two main schools of thought regarding PSA cutoff values held by professional clinical and laboratory organizations. One maintains that the appropriate cutoff value is 4 ng/mL, and the other maintains that there is no single cutoff value that is appropriate. Siemens Healthcare Diagnostics PSA assays have an optimum combination of sensitivity and specificity for prostate cancer at 4 ng/mL. For these assays, moving the cutoff from 4 ng/mL to 3 ng/mL is associated with great losses in specificity and modest gains in sensitivity. Regardless of your approach, Siemens provides a range of total PSA assays that can address your needs.

Introduction

Prostate cancer is one of the most prevalent types of cancer in men, and it is the second most commonly diagnosed cancer in American men. In the US, more than 192,000 men were expected to be diagnosed in 2009, and 27,360 to die of the disease.[1] The tools for early detection of prostate cancer include digital rectal exam (DRE), PSA testing, and biopsy. The advent of PSA testing has led to a substantial decrease in the percentage of patients diagnosed with advanced disease.[1] In the US, about 94 percent of men are diagnosed with organ-confined disease, which has a significantly better survival rate.[2]

There is no level of PSA below which a man is guaranteed not to have prostate cancer, but higher levels of PSA are associated with a higher risk for cancer (Table 1).[3]

Table 1. The risk of cancer in an average man (over age 50) with a negative DRE.[3]

PSA level (ng/mL)	Risk of positive biopsy (%)
0–2	10
2–4	15–25
4–10	17–32
>10	43–65

The definitive diagnosis of prostate cancer, however, is made by biopsy.[3] In addition to PSA results and DRE, clinical information such as patient age, family history, ethnicity, and comorbidities are used by clinicians to decide whether to proceed to biopsy (Figure 1).[3] Additionally, the American Urological Association and the National Comprehensive Cancer Network are now suggesting that the initial evaluation for prostate cancer be performed at age 40 instead of age 50. In younger men, a baseline PSA level above the median value for age has been shown to be associated with a risk of future prostate cancer. This evidence has been important in supporting the use of age-specific cutoffs.[1,3,4] In younger men, age-specific cutoffs are typically below 4 ng/mL.[3]

To improve standardization among PSA immunoassays, in 1999 the World Health Organization (WHO) adopted international standards for PSA (WHO 96/670) and free PSA (WHO 96/668). Siemens PSA assays on the ADVIA Centaur®, Dimension®, Dimension Vista®, and IMMULITE® platforms have calibration traceable to the WHO standard. While the international standards have improved the comparability between different manufacturers' assays, results from different manufacturers in PSA assays are still not interchangeable. This is due to the different antibodies and technologies used by different manufacturers in PSA assays.

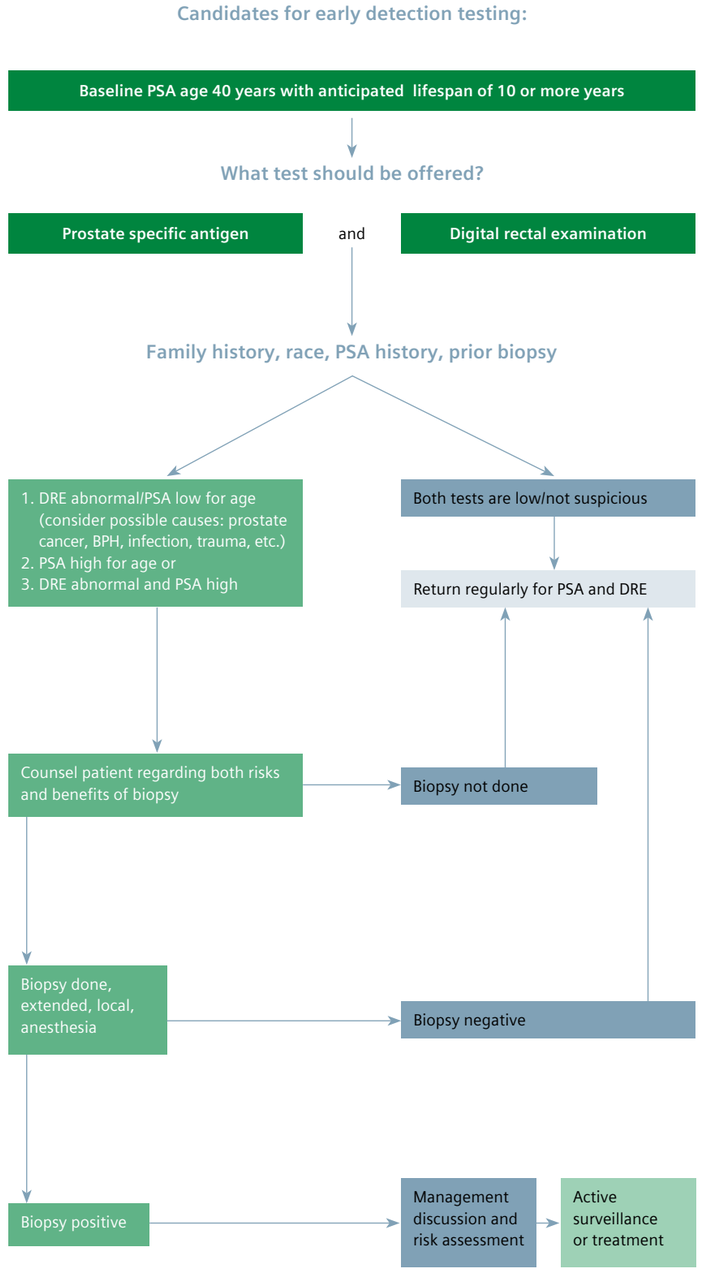

Figure 1. AUA early detection protocol.[3]

Guideline Recommendations from Laboratory and Clinical Organizations

For the majority of clinical tests used in diagnosis, the optimum cutoff is one that provides the best combination of sensitivity and specificity. The clinical study for the first PSA immunoassay approved by the FDA for use in the detection of prostate cancer in men >50 years of age in conjunction with DRE demonstrated an optimal cutoff of 4 ng/mL.[5] However, subsequent independent studies have suggested the use of lower cutoff values.[6] In general, changing cutoffs results in changes in both sensitivity and specificity, affecting the numbers of false-positive and false-negative test results. For PSA, increasing the cutoff decreases sensitivity and increases specificity, resulting in more false-negative results; whereas decreasing the cutoff increases sensitivity and decreases specificity, producing more false-positive results.

The consensus regarding the appropriate PSA cutoff value for triggering further evaluation is changing. There appear to be two approaches: (1) there is no evidence to support changing the cutoff from 4 ng/mL, and (2) no single cutoff is warranted because there is a range of PSA values of PSA at which a man can have cancer. The first approach is supported by the National Academy of Clinical Biochemistry (NACB) and the European Group on Tumour Markers (EGTM).[7] The second approach is supported by the American Urological Association (AUA), the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU).[1,3,8] The reasons behind each organization's approach are addressed in the following sections.

The National Academy of Clinical Biochemistry

The NACB contends that there is no compelling evidence that adoption of a cutoff lower than 4 ng/mL will benefit men being evaluated for prostate cancer:

"Given the controversy regarding the use of PSA values to detect very small tumors, reported benefits arising from lowering the clinical decision limit for biopsy lower than 4 µg/L are too uncertain to mandate any general recommendation. Cut-points lower than the commonly used 4 µg/L limit will increase sensitivity with a concomitant decrease in specificity unless other adjunctive tests or measures are employed to increase specificity. Conversely, use of clinical decision limits for PSA higher than 4.0 µg/L decreases the sensitivity, which results in the missed diagnoses of clinically significant tumors in men who might potentially benefit from early treatment."[7]

The European Group on Tumour Markers

The EGTM is skeptical of the value of age-specific cutoffs and cutoffs lower than 4 ng/mL:

"The use of age-specific reference ranges cannot be recommended yet, since no trials are available showing the efficacy of prostate biopsies for age-specific PSA decision points of concentrations lower than 4 ng/mL."[9]

The National Comprehensive Cancer Network

On the basis of the available evidence, the NCCN also shares the view that adoption of age-specific cutoffs is not warranted at this time. It recommends, however, that biopsies can be considered in men with PSA values in the range of 2.5 to 4 ng/mL but should be performed in men with PSA levels ≥10 ng/mL independent of DRE result.[1]

The American Urological Association

The AUA acknowledges that PSA levels above 4 ng/mL have a lower than desired sensitivity, and that while an obvious means of improving sensitivity is to have a lower threshold value for all men, a lower threshold is likely to exacerbate the problems associated with early detection such as increasing unnecessary biopsies and over-treatment. Increasing specificity by increasing the cutoff level could reduce unnecessary biopsies, but also runs the risk of missing high-grade cancers in older men and leading to over-detection of smaller volume/lower grade tumors in younger men. They advocate individualized risk assessment based on a variety of relevant risk factors:

"There is a continuum of risk at all values, with higher values of PSA associated with a higher risk of prostate cancer. Because of this, the AUA is not recommending a single threshold value which should prompt biopsy. The decision to proceed to biopsy should be primarily based 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 and comordidities."[3]

The European Association of Urology

The EAU argues that because "there are many different commercial test kits for measuring PSA, but no commonly agreed international standard exists… this means there is no universally accepted cut-off or upper limit."[8] Like the AUA and NCCN, it does not advocate a specific cutoff value.

Siemens PSA Assays and the Impact of Changing the Cutoff

Siemens PSA assays were FDA approved as aids in the detection of prostate cancer in conjunction with DRE for men 50 years and older, and for monitoring/managing prostate cancer. PSA is a prostate-specific analyte, but it is not a prostate cancer–specific analyte. As a result, all PSA assays have relatively low levels of specificity for prostate cancer. Furthermore, the lower the cutoff value used, the lower the level of specificity for prostate cancer. This is particularly important in preventing unnecessary biopsies, as only about one in four men biopsied have prostate cancer.[3] A cutoff lower than 4 ng/mL is likely to result in increases in the number of men undergoing unnecessary biopsies because of the associated decrease in specificity.

Siemens PSA assays on the ADVIA Centaur, IMMULITE, Dimension, and Dimension Vista platforms have calibration traceable to the WHO standard. These assays have an optimum combination of sensitivity and specificity for prostate cancer in a biopsy specimen at 4 ng/mL. While this cutoff is consistent with those of the other PSA manufacturers and the 2009 recommendations from the National Academy of Clinical Biochemistry, each lab should determine its own reference ranges and cutoff values.[7]

Clinicians and laboratorians need to determine which cutoff is appropriate for their patients, but should keep in mind that for Siemens PSA assays, changing the cutoff from 4 ng/mL to 3 ng/mL results in large comparative losses in specificity accompanied by very modest gains in sensitivity (Table 2). These losses in specificity would likely result in more unnecessary biopsies.

Conclusion

PSA is an important part of the early detection strategy for prostate cancer. Siemens PSA assays have an optimum combination of sensitivity and specificity for prostate cancer at 4 ng/mL. For these assays, moving the cutoff from 4 ng/mL to 3 ng/mL is associated with much lower specificity and modest gains in sensitivity. Regardless of your approach, Siemens provides a range of total PSA assays that can address your needs.

Table 2. A comparison of sensitivity and specificity at 4 ng/mL and 3 ng/mL for the ADVIA Centaur, Dimension, Dimension Vista, and IMMULITE PSA assays.

Analyzer	ADVIA Centaur		Dimension		Dimension Vista		IMMULITE[10]	
Cutoff	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
4 ng/mL	81.6%	27.4%	88.2%	27.5%	86.6%	32.6%	85.4%	48.9%
3 ng/mL	89.5%	13%	94%	17%	93.1%	21.1%	90%	39.4%

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