PSA Testing – New test delivers greater specificity

Benefit of screening as high as 30% mortality reduction – likely to increase with further follow-up, says ERSPC

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The potential benefits of screening for cancer are early detection, prompt treatment and a reduction in morbidity and mortality. However, clinicians and health policy decision makers have to balance this with the inevitable risk of overdiagnosis and the likelihood that some patients would incur unnecessary treatment. This is particularly relevant for prostate cancer (PCa) because of the lack of specificity in differentiating cancer from benign disease when PSA levels are elevated. Without the ability to discriminate, the benefits of screening for PCa with PSA remain controversial.

Over the last 20 years, the incidence of PCa has increased more than any other cancer, and it is now the second highest cause of cancer death in U.S. men. A man's risk increases sharply as he reaches the age of 50, with two in three cancers diagnosed in men over age 65.

The dilemma of screening versus overdiagnosis was brought into focus last year at the European Association of Urology's annual congress in Stockholm. The congress unveiled the findings of the world's largest study of PCa screening – conducted over 10 years in more than seven European countries – by the European Randomized Study of Screening for Prostate Cancer (ERSPC).[1] The results (published online by the *New England Journal of Medicine* at the same time as the congress) demonstrated for the first time that PSA screening could reduce mortality from prostate cancer by at least 20%.

A further analysis of their results, adjusted for non-attendance of the screening program and contamination (PSA testing of men in the control group) showed that PSA screening for prostate cancer actually reduced the risk of prostate cancer-specific death by up to 31%.[2] Throughout this long-term study, the PSA assay used at the screening centers has been the Hybritech assay – offered by Beckman Coulter, Inc.

Impact on resources

Novel markers have been urgently needed for the early detection and reliable diagnosis of PCa, because current PSA blood tests have limited positive predictive value. While PSA testing has led to a sharp decrease in the prevalence of advanced stages of prostate, we have seen a corresponding rise in potentially unnecessary biopsies and the risk from treating low-risk PCa patients. Following a prostate needle biopsy, only 20 to 30% of men with serum PSA levels from 2 to 4 ng/mL and 30 to 45% with serum PSA levels from 4 to 10 ng/mL are found to have PCa.[1,2,3] This means over two thirds have to undergo an invasive test unnecessarily, which is not only stressful but a waste of resources.

The ERSPC findings have had a significant impact on medical thinking, particularly with the current interest in more conservative PCa management approaches such as "active surveillance". Separate ERSPC findings already confirm that approximately 30% of detected PCa actually have non-aggressive features and are possibly 'indolent'. The patients will therefore die from other causes, not prostate cancer.[1]

If clinicians are to wait before sending certain patients with PSA levels < 10 ng/mL for biopsy, they must be sure indolent tumours can be more accurately identified at diagnosis and that robust clinical tools can be developed that precisely signal the need for intervention.

p2PSA – a promising marker

For many years, Beckman Coulter has been searching to find more specific biomarkers. The use of the more specific percent free PSA (%fPSA) has already been shown to offer significantly improved cancer specificity in the 4 to 10 ng/mL range.[1,2,3,4]

Free PSA is made up of several distinct molecular forms that appear to be diagnostically significant and unique, indicating an association with either BPH or prostate cancer.[1,2] Beckman Coulter has identified several isoforms of free PSA in the blood of PCa patients. When using a unique monoclonal antibody (MAb), an increase in individual isoforms – in particular [-2]proPSA – was associated with PCa.[1,2,3,4,5] The use of this antibody further demonstrated greater immunohistochemical (IHC) staining in prostate tumour tissue than in benign prostate tissue.[1,2]

This increased specificity of the [-2]proPSA isoform, measured with the Access Hybritech p2PSA* laboratory assay, demonstrates its potential in the detection of PCa when assessing PSA levels between 2 and 10 ng/mL. Several retrospective studies (using archived samples) have shown that ratios of total proPSA and p2PSA to fPSA (%proPSA and %p2PSA, respectively) were more PCa-specific than combinations of total PSA and fPSA for PCa detection.[8,9,15,16,17]

[-2]proPSA levels have been correlated with clinically significant PCa, including more advanced pathologic stage, higher tumour volume and higher tumour grade. [-2]proPSA has also been shown to improve discrimination where there is particular diagnostic uncertainty, such as with patients with %fPSA > 25 or those patients with total PSA levels of 2 to 4 ng/mL.[13]

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Levels of proPSA may also be useful when patients are being considered for active surveillance. In a group of 71 men who underwent annual surveillance biopsies, the ratio of serum p2PSA/%fPSA was found to be significantly higher in those who developed aggressive features in their biopsy specimen (Gleason score ≥ 7). The [-5,7] proPSA staining was greater in the benign area adjacent to the biopsy in those 39 men with an unfavourable biopsy profile.[1] All of these studies used archived samples.

Improving biomarker assessment

To help improve the specificity of PSA biomarkers, Beckman Coulter has introduced a mathematical formula called *Prostate Health Index (phi)* that combines a reading of Access Hybritech PSA, fPSA and p2PSA levels and has been validated in men with PSA levels from 2 to 10 ng/mL. The index was launched in Europe at the end of 2009.

The new p2PSA test can be easily performed in the laboratory using the automated Beckman Coulter family of Access immunoassay systems and run with traditional PSA and free PSA tests. The extra dimension offered by the *Prostate Health Index* means that the lab can provide the clinician with an automatic calculation from the index using the PSA, free PSA and p2PSA test results. The *phi* result gives the probability of prostate cancer. It does this by providing a significant increase in specificity over total, free PSA, or %fPSA while maintaining the accepted cancer detection rate (Table 1).

Patients do not always appreciate that many PCa (a significant number of which are high grade) are found in men with PSA levels considered to be in the "normal" range of 2 to 4 ng/mL range (Figure 2).[1] The availability of a laboratory test with a high specificity for PCa even in this challenging range offers the potential to identify early-stage PCa for these men.

Effectiveness of p2PSA and *Prostate Health Index (phi)*

The first prospective study looking at the effectiveness of p2PSA and *phi* for prostate cancer screening in men has recently been completed.[1]

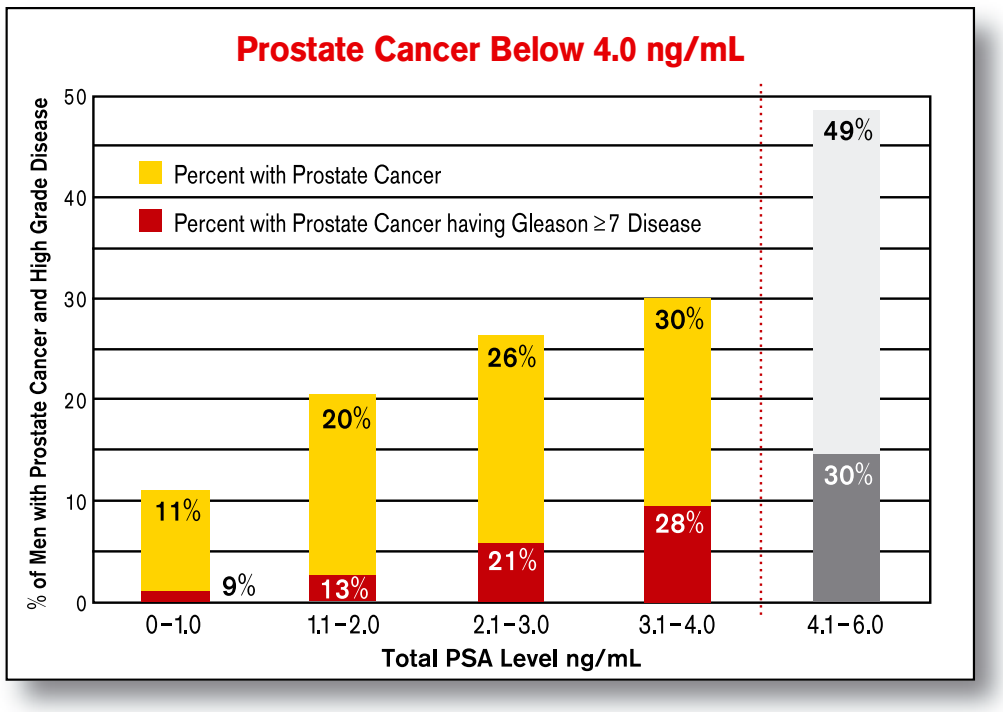

*Figure 1: Proportion and severity of prostate cancer where total PSA < 4.0 ng/mL.****

The relationship between p2PSA and prostate cancer detection was examined in 2034 men undergoing prostate screening. The study assessed the accuracy of total PSA, the ratio of free PSA (fPSA) to total PSA (%fPSA), the ratio of p2PSA to fPSA (%p2PSA) and the *phi* formula in predicting prostate cancer among men from the study with PSA levels of 2.5-10 ng/mL and non-suspicious digital rectal examination (DRE) who underwent prostate biopsy. Results were generated using the Access Hybritech PSA, free PSA, and p2PSA assays.

Maintaining the clinical sensitivity of prostate cancer at 88.5%, the results showed that p2PSA provides improved discrimination between prostate cancer and benign disease. Despite similar total PSA levels, it was seen that both %fPSA and %p2PSA distinguished between positive and negative biopsy results. On receiver operating characteristic (ROC) analysis, %p2PSA outperformed both PSA and %fPSA for differentiating between prostate cancer and benign disease.

Improving patient quality of life

The ERSPC study demonstrated for the first time the value of PSA screening, showing it has the potential to reduce PCa mortality by more than 30% and likely more with further planned follow-up of study participants.[2] At the same time, the study highlighted that the price of this reduction would continue to be overdiagnosis until a more specific testing regime could be developed. The risk of the unnecessary treatment of indolent cancers therefore remained significant.

The use of free PSA (%fPSA) rather than total serum PSA is known to significantly improve PCa detection rates in the 4 to 10 ng/mL range.[7,8,9,10] By measuring levels of proPSA isoforms specifically associated with PCa, in particular serum[-2]proPSA, this is likely to further improve clinical assessment because [-2] proPSA is better able to discriminate between PCa and benign disease.[20]

However, when combined with Access Hybritech PSA and free PSA in the new *phi* index, Access Hybritech p2PSA* promises to deliver superior accuracy in assessing the need for a prostate biopsy, particularly at low levels of total PSA (in the 2-10 ng/mL range). The use of the new assay – with its ability to increase clinical specificity for PCa – also offers the potential to reduce the number of negative biopsies.

The promise of this new marker used in the index to discriminate between PCa and benign disease heralds a significant step forward for PCa patients and their families. It appears to offer clinicians a way of reducing both the number of invasive biopsies that turn out to be negative, and unnecessary treatment for some patients. Finding a more definitive way of diagnosing PCa using PSA screening is beneficial to patients, as well as being economically attractive to health policy makers.

* In development for US market, pending FDA approval

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*** Adapted by Beckman Coulter

Thompson, I.M., Ankerst. D.P., Chi, C., Goodman, P.J., Tangen, C. M., Lucia, M. S., Feng, Z., Parnes, H. L., Coltman, C.A. Assessing prostate cancer risk: Results from the Prostate Cancer Prevention Trial. J of National Cancer Institute 2006 Apr 19; (8): 529-535.

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Beckman Coulter *phi* Range (Hybritech Calibration of PSA, free PSA)	Probability of Cancer	95% Confidence Interval
0 – 21	Low 8.4%	1.9% – 16.1%
21 – 40	Moderate 21.0%	17.3% – 24.6%
greater than 40	High 44.0%	36.0% – 52.9%

Interpretation of *phi* can help distinguish men with low, moderate and high probability of having prostate cancer.

% Clinical Sensitivity	*phi* Cut-off Hybritech calibration	% Clinical Specificity
95	21.13	18.2
90	23.82	30.4
88	25.0	33.6
85	26.34	38.8

For example, a *phi* of 25 corresponds to 88% clinical sensitivity and 33.6% clinical specificity.

*Table 1: Probability of prostate cancer based on phi in patients with total PSA 2-10 ng/mL.***