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Prostate Health Index (phi) using [-2]proPSA improves detection of prostate cancer preferentially identifying aggressive cancers

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Objectives

The benefit of screening for prostate cancer (PCa) using total prostate-specific antigen (tPSA) as the biochemical marker is a matter of intense debate, due to the relatively low clinical specificity of tPSA leading to serious drawbacks such as overdiagnosis and overtreatment. New biomarkers that could improve the specificity for PCa detection are highly desirable. Previous studies showed that a molecular isoform of PSA ([-2]proPSA) could improve the clinical specificity for the detection of PCa compared to tPSA and free PSA (fPSA) [1,2]. Beckman Coulter recently developed an innovative "Prostate Health Index" or "*phi*" which combines tPSA, fPSA and [-2]proPSA results [3]. This four center study was set up to confirm previously demonstrated clinical performance of *phi* for the detection of PCa [3]. The results of an interim analysis are presented in this poster.

Material and Methods

A total of 902 patients with tPSA values between 1.6 – 8.0 ng/mL (WHO-calibrated), 446 with, 456 without PCa, underwent ≥10 core biopsies in four different sites were enrolled in the study. A tPSA range of 1.6 – 8.0 ng/mL with a WHO-calibrated tPSA Access assay corresponds to a range of 2 – 10 ng/mL with a Hybritech- calibrated tPSA Access assay. Similarly, the classical decision point of 4.0ng/mL in Hybritech-calibrated assay corresponds to 3.1ng/mL with a WHO-calibrated assay. Serum samples were prepared from blood drawn prior to DRE. Serum samples from the enrolled patients were prepared within 3 hours of the blood draw then stored frozen at -20°C or -80C° [4]. The serum concentrations of tPSA, fPSA and [-2]proPSA were measured with Beckman Coulter Access immunoassays on an Access2 or Unicel Dxl 800 instrument. The Prostate Health Index was calculated using the following formula: (p2PSA/fPSA)*√tPSA [3]. ROC curves were plotted to compare the clinical performances of tPSA, %fPSA and *phi* for the detection of PCa. The relationship with PCa aggressiveness was performed on 352 patients for which the biopsy Gleason score information was available. Based on this information, the patients were grouped as "aggressive PCa" for patients with biopsy Gleason score of 7 and above (GS ≥ 7) or " less aggressive" PCa for patients with biopsy Gleason score of 6 (GS < 7).

Results.

• Detection of PCa for patients with tPSA > 1.6 and < 8.0 ng/mL

Patients (n)	902
Diagnosis (n)	
No PCa	**456**
PCa	**446**

Test (Median)	PCa n=446	Non-PCa n=456	Significance§ (p)
tPSA (ng/mL)	4.83	4.53	0.008
%fPSA	14.04	16.60	**<0.0001**
p2PSA (pg/mL)	15.15	12.70	**<0.0001**
phi	56.47	38.38	**<0.0001**

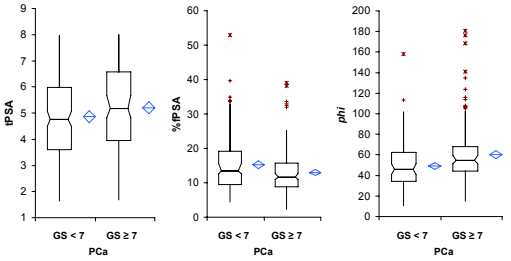
Test	Area ROC	95% CI	Significance§ (p)
tPSA (ng/mL)	0.53	0.46 to 0.61	-
%fPSA	0.58	0.51 to 0.65	0.3063*
phi	**0.72**	0.66 to 0.79	**<0.0001****

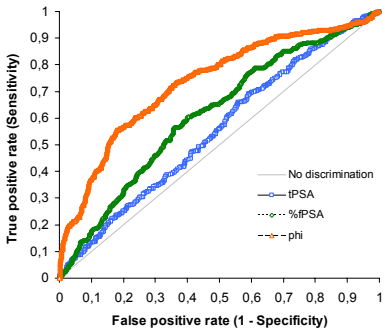
* %fPSA vs tPSA
** %fPSA vs phi
§: Mann-Whitney test

• Relationship with PCa aggressiveness (biopsy Gleason score)

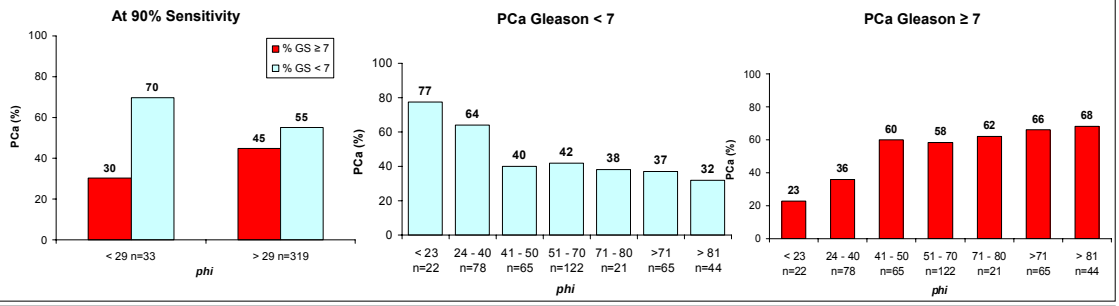
Test (Median)	GS ≥ 7 n=186	GS < 7 n=166	Significance§ (p)
tPSA (ng/mL)	5.17	4.76	0.004
%fPSA	11.70	13.46	**<0.002**
phi	54.89	46.06	**<0.0001**

§: Mann-Whitney test





• Proportion of Gleason ≥ 7 PCa detected with *phi*



Results

• The Prostate Health Index significantly improves the detection of PCa
Significant higher median values for tPSA, p2PSA and *phi* are observed for the patients with PCa compared with patients without PCa. The median value of %fPSA was significantly lower in PCa patients compared with with patients without PCa. The ROC curve analysis showed that *phi* (AUC=0.72, 95% CI: 0.66 – 0.79) provided significantly (p < 0.0001) better clinical performance to detect PCa compared to tPSA (AUC=0.53, 95% CI: 0.46 – 0.61) and %fPSA (AUC=0.58, 95% CI: 0.51 – 0.65). The difference between the ROC AUC of %fPSA and tPSA did not reach statistical significance (p=0.3063). Interestingly, similar results were observed when the analysis was performed in men with tPSA < 3.1ng/mL (data not shown). The percentage of positive biopsies is increasing with the *phi* index values. In the group of patients with *phi* below 20 (n=78), only 26% had a positive biopsy while patients with *phi* > 70 (n=113), had a positive biopsy in 83.3% of the cases. An improvement in specificity at 90% sensitivity was observed for the *phi* (cut off 29; specificity 33%) as compared for tPSA (cut off 3.02; specificity 13%) and %fPSA (cut off 22.8; Specificity 17%).

• Relationship with PCa aggressiveness (biopsy Gleason score)
The mean and median values of tPSA, %fPSA and *phi* were significantly different between the group of patients with aggressive PCa (Gleason ≥ 7) compared to the group of patients with less aggressive PCa (Gleason < 7). Higer values were observed for tPSA and *phi* for patients with aggressive PCa (Gleason ≥ 7), while lower values for %fPSA was shown for this patient group.

• Increasing proportion of aggressive PCa (Gleason ≥ 7) detected at high *phi* values
Analysis of the biopsy Gleason score of the PCa detected with the *phi* shows that a greater proportion of aggressive PCa (Gleason ≥ 7) are detected at high *phi* values. 68% of the PCa detected with *phi* > 81 (n=44) had a biopsy Gleason score of 7 or above. The majority (77%) of the PCa detected with *phi* values < 23 (n=22) were Gleason <7.

• The majority of PCa missed with *phi* at 90% sensitivity are less aggressive PCa (Gleason < 7)
When clinical sensitivity is set at 90% (*phi* cut off: 29), the majority (70%) of the 10% of PCa (n=33) not detected are Gleason < 7 and 30% are Gleason ≥ 7. If similar sensitivity is defined for tPSA (cut off 3.02) or for %fPSA (cut off: 22.78) more aggressive PCa would be missed (41% for tPSA and 33% for %fPSA).

Conclusions.

The results of this multicenter study indicate that *phi* has superior clinical performance in detecting PCa in the tPSA range of 1.6 – 8.0 ng/mL (WHO calibration) compared to tPSA or %fPSA. The *phi* index was the best predictor of prostate cancer compared to tPSA and %fPSA. *phi* tends to preferentially detect aggressive PCa. At high sensitivity, PCa missed are mainly Gleason < 7. These data confirmed previously published observation on the benefit of the [-2]proPSA and the *phi* index for the PCa detection. These results warrant further investigations to explore the relationship between the *phi* index and PCa aggressiveness, and especially the analysis of the pathological Gleason, prostate and tumor volume in relation with the *phi* would be interesting. Further analysis of the results will be required to define the optimal settings for *phi* implementation in routine practice.

References.

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