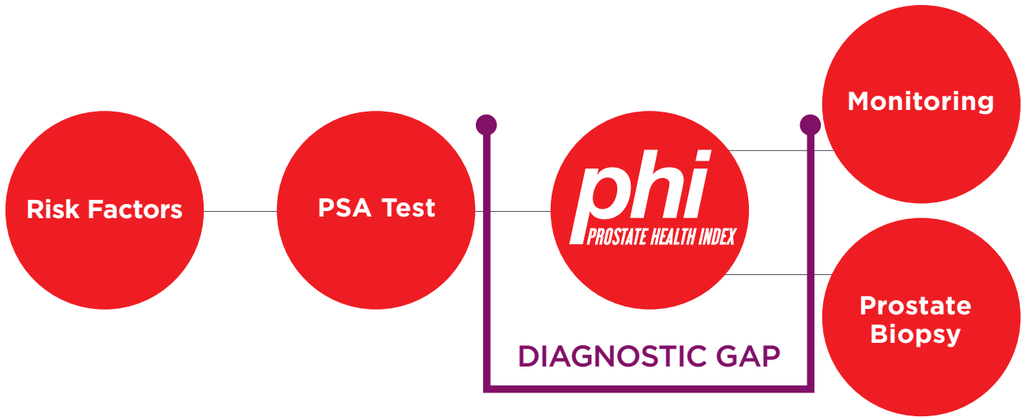
“Compared with PSA-only screening, the use of a *phi* test can substantially reduce the number of negative biopsies and improve the cost-effectiveness of prostate cancer detection.”

— Heijnsdijk E.A. Value Health 2016; 19(2): 153-157.



PUBLISHED SCIENTIFIC EVIDENCE ON THE USE OF PROSTATE HEALTH INDEX 2014–2018

Prostate Health Index *(phi)*

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Urologic Clinics of North America. 2016; 43(1): 1-6.

The Prostate Health Index: its utility in prostate cancer detection.

Authors: Lepor A, Catalona W, Loeb S.

Key Point:

- The Prostate Health Index *(phi)* is a mathematical formula that combines total, free, and proPSA
- The *phi* test is more specific for the detection of clinically significant prostate cancer than free and/or total PSA
- The *phi* test was approved by the U.S. FDA in 2012 and is included in the National Comprehensive Cancer Network Guidelines for early prostate cancer detection
- Increasing *phi* scores predict a greater risk of high-risk pathology and biochemical recurrence after radical prostatectomy
- A *phi* test performed at the initiation and during the course of active surveillance predicts subsequent biopsy reclassification

"Numerous large, prospective studies from geographically diverse regions have consistently demonstrated that *phi* is more specific for prostate cancer detection than existing standard reference tests of total and free PSA."

— Lepor A, et al. 2016 Urologic Clinics of North America.

BJU International. 2016; 117: 72-9.

The percentage of prostate-specific antigen (PSA) isoform [−2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged ≤ 65 years.

Authors: Boegemann M, Stephan C, Cammann H, et al.

Objectives:

To prospectively test the diagnostic accuracy of the percentage of prostate specific antigen (PSA) isoform [−2]proPSA (%p2PSA) and the Prostate Health Index *(phi),* and to determine their role for discrimination between significant and insignificant prostate cancer at initial and repeat prostate biopsy in men aged ≤65 years.

Patients and methods:

The diagnostic performance of %p2PSA and *phi* were evaluated in a multicenter study. In all, 769 men aged ≤65 years scheduled for initial or repeat prostate biopsy were recruited in four sites based on a total PSA (t-PSA) level of 1.6–8.0 ng/mL World Health Organization (WHO) calibrated (2–10 ng/mL Hybritech-calibrated). Serum samples were measured for the concentration of t-PSA, free PSA (f-PSA) and p2PSA with Beckman Coulter immunoassays on Access-2 or DxI800 instruments. *phi* was calculated as (p2PSA/f-PSA × √t-PSA). Uni- and multivariable logistic regression models and an artificial neural network (ANN) were complemented by decision curve analysis (DCA).

Results:

In univariate analysis, %p2PSA and *phi* were the best predictors of prostate cancer detection in all patients (area under the curve [AUC] 0.72 and 0.73, respectively), at initial (AUC 0.67 and 0.69) and repeat biopsy (AUC 0.74 and 0.74). t-PSA and %f-PSA performed less accurately for all patients (AUC 0.54 and 0.62). For detection of significant prostate cancer (based on Prostate Cancer Research International Active Surveillance [PRIAS] criteria) the %p2PSA and *phi* equally demonstrated best performance (AUC 0.70 and 0.73) compared with t-PSA and %f-PSA (AUC 0.54 and 0.59). In multivariate analysis of *phi*, we added to a base model of age, prostate volume, digital rectal examination and t-PSA and %f-PSA. *phi* was strongest in predicting prostate cancer in all patients, at initial and repeat biopsy and for significant prostate cancer (AUC 0.73, 0.68, 0.78 and 0.72, respectively). In DCA for all patients the ANN showed the broadest threshold probability and best net benefit. *phi* as single parameter and the base model + *phi* were equivalent with threshold probability and net benefit nearing those of the ANN. For significant cancers the ANN was the strongest parameter in DCA.

Conclusion:

The present multicenter study showed that %p2PSA and *phi* have a superior diagnostic performance for detecting prostate cancer in the PSA range of 1.6–8.0 ng/mL compared with t-PSA and %f-PSA at initial and repeat biopsy and f or predicting significant prostate cancer in men aged ≤65 years. They are equally superior for counselling patients before biopsy.

BJU International. 2016; 117(3): 409-17.

Improving multivariable prostate cancer risk assessment using the Prostate Health Index.

Authors: Foley RW, Gorman L, Sharifi N, et al.

Objectives:

To analyze the clinical utility of a prediction model incorporating both clinical information and a novel biomarker, p2PSA, in order to inform the decision for prostate biopsy in an Irish cohort of men referred for prostate cancer assessment.

Patients and methods:

Serum isolated from 250 men from three tertiary referral centers with pre-biopsy blood draws was analyzed for total prostate-specific antigen (PSA), free PSA (fPSA) and p2PSA. From this, the Prostate Health Index *(phi)* score was calculated (*phi* = (p2PSA/fPSA)*√tPSA). The men's clinical information was used to derive their risk according to the Prostate Cancer Prevention Trial (PCPT) risk model. Two clinical prediction models were created via multivariable regression consisting of age, family history, abnormality on digital rectal examination, previous negative biopsy and either PSA or *phi* score, respectively. Calibration plots, receiver-operating characteristic (ROC) curves and decision curves were generated to assess the performance of the three models.

Results:

The PSA model and *phi* model were both well calibrated in this cohort, with the *phi* model showing the best correlation between predicted probabilities and actual outcome. The areas under the ROC curve for the *phi* model, PSA model and PCPT model were 0.77, 0.71 and 0.69, respectively, for the prediction of prostate cancer (PCa) and 0.79, 0.72 and 0.72, respectively, for the prediction of high grade PCa. Decision-curve analysis showed a superior net benefit of the *phi* model over both the PSA model and the PCPT risk model in the diagnosis of PCa and high grade PCa over the entire range of risk probabilities.

Conclusion:

A logical and standardized approach to the use of clinical risk factors can allow more accurate risk stratification of men under investigation for PCa. The measurement of p2PSA and the integration of this biomarker into a clinical prediction model can further increase the accuracy of risk stratification, helping to better inform the decision for prostate biopsy in a referral population.

Journal of Urology. 2015;193(4):1163-9.

The Prostate Health Index selectively identifies clinically significant prostate cancer.

Authors: Loeb S, Sanda MG, Broyles D, et al.

Purpose:

The Prostate Health Index *(phi)* is a new test combining total, free and [-2]proPSA into a single score. It was recently approved by the FDA and is now commercially available in the U.S., Europe and Australia. We investigate whether *phi* improves specificity for detecting clinically significant prostate cancer and can help reduce prostate cancer over diagnosis.

Materials and methods:

From a multicenter prospective trial, we identified 658 men age 50 years or older with prostate-specific antigen 4 to 10 ng/ml and normal digital rectal examination who underwent prostate biopsy. In this population we compared the performance of prostate specific antigen, % free prostate specific antigen, [-2]proPSA and *phi* to predict biopsy results and, specifically, the presence of clinically significant prostate cancer using multiple criteria.

Results:

The Prostate Health Index was significantly higher in men with Gleason 7 or greater and 'Epstein significant' cancer. On receiver-operating characteristic analysis, *phi* had the highest AUC for overall prostate cancer (AUCs *phi* 0.708, percent free prostate specific antigen 0.648, [-2]proPSA 0.550 and prostate specific antigen 0.516), Gleason 7 or greater (AUCs *phi* 0.707, percent free prostate specific antigen 0.661, [-2]proPSA 0.558, prostate specific antigen 0.551) and significant prostate cancer (AUCs *phi* 0.698, percent free prostate-specific antigen 0.654, [-2]proPSA 0.550, prostate-specific antigen 0.549). At the 90% sensitivity cut point for *phi* (a score less than 28.6), 30.1% of patients could have been spared an unnecessary biopsy for benign disease or insignificant prostate cancer, compared to 21.7% using percent free prostate-specific antigen.

Conclusions:

The new *phi* test outperforms its individual components of total, free and [-2]proPSA for the identification of clinically significant prostate cancer. *Phi* may be useful as part of a multivariable approach to reduce prostate biopsies and over diagnosis.

Urology. 2016;90:136-40.

Prostate Health Index (*phi*) predicts high-stage pathology in African-American men.

Authors: Schwen ZR, Tosoian JJ, Sokoll LJ, et al.

Objectives:

To evaluate the association between the Prostate Health Index *(phi)* and adverse pathology in a cohort of African-American (AA) men undergoing radical prostatectomy (RP).

Methods:

Eighty consecutive AA men with PSA of 2–10 ng/ml underwent measurement of PSA, free PSA (fPSA), and p2PSA prior to RP. *phi* was calculated as [(p2PSA/fPSA) x (PSA)½]. Biomarker association with pT3 disease was assessed using logistic regression, and covariates were added to a baseline multivariable model including digital rectal examination (DRE). Biomarker ability to predict pT3 disease was measured using the area under the ROC curve (AUC).

Results:

Sixteen men (20%) demonstrated pT3 disease on final pathology. Mean age, PSA and %fPSA were similar in men with and without pT3 disease (all p>0.05), while *phi* was significantly greater in men with pT3 disease (mean 57.2 vs. 46.6, p=0.04). Addition of *phi* to the baseline multivariable model improved discriminative ability by 12.9% (p=0.04) and yielded greater diagnostic accuracy than models including other individual biomarkers.

Conclusions:

In African-American men with PSA of 2–10 ng/ml, *phi* was predictive of pT3 prostate cancer and may help to identify men at increased risk of adverse pathology. Additional studies are needed to substantiate these findings and identify appropriate thresholds for clinical use.

J Urology. 2015; 193(4S): e56.

MP6-06: Prostate Health Index predicts upgrading of men on 5-alpha reductase inhibitors.

Authors: Crawford ED, Arangua P, Jones C, et al.

Introduction and objectives:

A single transrectal biopsy (TRUS) is often insufficient to accurately identify low-risk prostate cancer (PCa) patients for active surveillance, and resampling is frequently recommended for more accurate classification. Although recent studies have suggested that the Beckman Coulter Prostate Health Index *(phi)* is a significant predictor of high-grade PCa (Gleason score ≥7), these studies have not included patients on 5-alpha reductase inhibitors (5ARI). We performed a pilot study to determine whether *phi* predicts upgrading and upstaging on resampling for men on 5ARI.

Methods:

Forty seven patients elected template-guided transperineal mapping biopsy (TPMB) after their initial TRUS were negative or detected a low risk cancer. All patients had 5ARI prior to TPMB in an effort to reduce prostate size. Prostate specific antigen (tPSA), free PSA (fPSA), and p2PSA were measured using Hybritech calibration from serum samples drawn prior to TPMB. We calculated percent fPSA (%fPSA)=free PSA/tPSA×100 and *phi*=(p2PSA/fPSA)×√(tPSA). Patients were upgraded when the Gleason score increased by ≥ 1 from TRUS to TPMB. Patients were upstaged if: 1) unilateral on TRUS changed to bilateral in TPMB or 2) the increase in number of positives cores was ≥3 from TRUS to TPMB. Wilcoxon rank sum test and logistic regression analysis (LRA) were used to determine the odds ratio (OR) and statistical significance (≤0.05). Receiver operating curve (ROC) analysis was done to compare performance of *phi*.

Results:

The mean age, tPSA, %p2PSA, and *phi* of patients were 64 yr, 7.4 ng mL−1, 6.32%, and 37, respectively. Among the 47 patients, 24 had both positive and 4 had both negative TRUS and TPMB. 11 patients had positive TRUS and negative TPMB while 8 patients had negative TRUS and positive TPMB. 15/47 patients were upgraded. *phi* (46.32 vs. 28.21; p=0.0029) predicted upgrading. In the LRA, *phi* (OR=1.1, p=0.01) also predicted patients upgraded. In ROC analysis, there were no differences in area under the curve (AUC) for *phi* (0.77), tPSA (0.68), and %fPSA (0.71). Additionally, 25/47 patients were upstaged by *phi* (median 45.33 vs. 24.54; p=0.0001). *phi* (OR=1.1, p=0.0018) also predicated upstaging in the LRA. AUC of *phi* (0.82) was significantly different than AUC of tPSA (0.64, p=0.025), but not AUC of %fPSA (0.65). The main limitation of this study is the relative small sample size.

Conclusions:

Our study demonstrates the potential clinical utility of *phi* for identification of high risk PCa patients on 5ARI. Patients with high *phi* who have favorable features on TRUS may choose TPMB before electing surveillance or watchful waiting.

European Urology Focus. 2015; 1(2): 185-90.

Comparison of two prostate cancer risk calculators that include the Prostate Health Index.

Authors: Roobol M, Vedder MM, Nieboer D, et al.

Background:

Risk prediction models for prostate cancer (PCa) have become important tools in reducing unnecessary prostate biopsies. The Prostate Health Index *(phi)* may increase the predictive accuracy of such models.

Objectives:

To compare two PCa risk calculators (RCs) that include *phi*.

Design, setting and participants:

We evaluated the predictive performance of a previously developed *phi*-based nomogram and updated versions of the European Randomized Study of Screening for Prostate Cancer (ERSPC) RCs based on digital rectal examination (DRE): RC3 (no prior biopsy) and RC4 (prior biopsy). For the ERSPC updates, the original RCs were recalibrated and *phi* was added as a predictor. The *phi*-updated ERSPC RCs were compared with the Lughezzani nomogram in 1,185 men from four European sites. Outcomes were biopsy-detectable PC and potentially advanced or aggressive PCa, defined as clinical stage >T2b and/or a Gleason score ≥7 (clinically relevant PCa).

Results and limitations:

The *phi*-updated ERSPC models had a combined area under the curve for the receiveroperating characteristic (AUC) of 0.72 for all PCa and 0.68 for clinically relevant PCa. For the Lughezzani *phi*-based nomogram, AUCs were 0.75 for all PCa and 0.69 for clinically relevant PCa. For men without a prior biopsy, *phi*-updated RC3 resulted in AUCs of 0.73 for PCa and 0.66 for clinically relevant PCa. Decision curves confirmed these patterns, although the number of clinically relevant cancers was low.

Conclusion:

Differences between RCs that include *phi* are small. Addition of *phi* to an RC leads to further reductions in the rate of unnecessary biopsies when compared to a strategy based on prostate-specific antigen measurement.

Patient summary:

Risk prediction models for prostate cancer have become important tools in reducing unnecessary prostate biopsies. We compared two risk prediction models for prostate cancer that include the Prostate Health Index. We found that these models are equivalent to each other, and both perform better than the prostate-specific antigen test alone in predicting cancer.

Journal of Urology. 2015; 194(1): 65-72.

Multicenter evaluation of the Prostate Health Index to detect aggressive prostate cancer in biopsy-naïve men.

Authors: de la Calle C, Patil D, Wei JT, et al.

Purpose:

We evaluated the ability of *phi* to discriminate aggressive prostate cancer from indolent or no cancer in a biopsy-naïve population.

Materials and methods:

Two independent prospective cohorts of 561 and 395 subjects, respectively, with no prior prostate biopsy who were enrolled at different clinical sites, were used to validate the results. We compared the diagnostic specificity of *phi* to pre-biopsy total and percent free prostate-specific antigen using prostate biopsy results. We also determined the optimal *phi* threshold to discriminate aggressive prostate cancer (Gleason score 7 or greater) from indolent or no prostate cancer (Gleason score 6 or less).

Results:

In the primary cohort, higher *phi* values were significantly associated with a Gleason score of 7 or greater. The AUC to detect aggressive prostate cancer was 0.815. At 95% sensitivity *phi* specificity was 36.0% vs. 17.2% and 19.4% for total and percent free prostate-specific antigen, respectively. At 95% sensitivity for detecting aggressive prostate cancer, the optimal *phi* cutoff was 24, which would help avoid 41% of unnecessary biopsies. A cutoff of 24 led to 36% biopsies avoided with few aggressive cancers missed. These results were confirmed in the validation cohort.

Conclusions:

The *phi* detected aggressive prostate cancer with better specificity than total and percent free prostate-specific antigen in a biopsy-naïve population. It could be a useful tool to decrease unnecessary prostate biopsies.

BJU International. 2015; 115: 537-45.

Clinical performance of the Prostate Health Index *(phi)* for the prediction of prostate cancer in obese men: data from the PROMEtheuS project, a multicentre European prospective study.

Authors: Abrate A, Lzaaen M, Lughezzani G, et al.

Objectives:

To test serum prostate-specific antigen (PSA) isoform [-2]proPSA (p2PSA), p2PSA/free PSA (%p2PSA) and Prostate Health Index *(phi)* accuracy in predicting prostate cancer in obese men and to test whether *phi* is more accurate than PSA in predicting prostate cancer in obese patients.

Patients and methods:

The analysis consisted of a nested case-control study from the pro-PSA Multicentric European Study (PROMEtheuS) project. The study is registered at http://www.controlled-trials.com.libproxy.lib.unc.edu/ISRCTN04707454. The primary outcome was to test sensitivity, specificity and accuracy (clinical validity) of serum p2PSA, %p2PSA and *phi*, in determining prostate cancer at prostate biopsy in obese men [body mass index (BMI) ≥30 kg/m2], compared with total PSA (tPSA), free PSA (fPSA) and fPSA/tPSA ratio (%fPSA). The number of avoidable prostate biopsies (clinical utility) was also assessed. Multivariable logistic regression models were complemented by predictive accuracy analysis and decision curve analysis.

Results:

Of the 965 patients, 383 (39.7%) were normal weight (BMI <25 kg/m2), 440 (45.6%) were overweight (BMI 25–29.9 kg/m2) and 142 (14.7%) were obese (BMI ≥30 kg/m2). Among obese patients, prostate cancer was found in 65 patients (45.8%), with a higher percentage of Gleason score ≥7 diseases (67.7%). PSA, p2PSA, %p2PSA and *phi* were significantly higher and %fPSA significantly lower in patients with prostate cancer (P<0.001). In multivariable logistic regression models, *phi* significantly increased the accuracy of the base multivariable model by 8.8% (P=0.007). At a *phi* threshold of 35.7, 46 (32.4%) biopsies could have been avoided.

Conclusion:

In obese patients, *phi* is significantly more accurate than current tests in predicting prostate cancer.

BJU Int 120(1): 61-68.

Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer.

Loeb, S., S. S. Shin, et al. (2017)

Objective:

To examine the use of the Prostate Health Index (*phi*) as a continuous variable in multivariable risk assessment for aggressive prostate cancer in a large multicentre US study.

Materials and methods:

The study population included 728 men, with prostate-specific antigen (PSA) levels of 2–10 ng/mL and a negative digital rectal examination, enrolled in a prospective, multi-site early detection trial. The primary endpoint was aggressive prostate cancer, defined as biopsy Gleason score >/=7. First, we evaluated whether the addition of *phi* improves the performance of currently available risk calculators (the Prostate Cancer Prevention Trial [PCPT] and European Randomised Study of Screening for Prostate Cancer [ERSPC] risk calculators). We also designed and internally validated a new PHI-based multivariable predictive model, and created a nomogram.

Results:

Of 728 men undergoing biopsy, 118 (16.2%) had aggressive prostate cancer. The *phi* predicted the risk of aggressive prostate cancer across the spectrum of values. Adding *phi* significantly improved the predictive accuracy of the PCPT and ERSPC risk calculators for aggressive disease. A new model was created using age, previous biopsy, prostate volume, PSA and *phi*, with an area under the curve of 0.746. The bootstrap-corrected model showed good calibration with observed risk for aggressive prostate cancer and had net benefit on decision-curve analysis.

Conclusion:

Using *phi* as part of multivariable risk assessment leads to a significant improvement in the detection of aggressive prostate cancer, potentially reducing harms from unnecessary prostate biopsy and overdiagnosis.

Prostate 77(11): 1221-1229.

Prostate Health Index significantly reduced unnecessary prostate biopsies in patients with PSA 2–10 ng/mL and PSA >10 ng/mL: Results from a Multicenter Study in China.

Authors: Na, R., D. Ye, et al. (2017)

Background:

The performance of prostate health index *(phi)* in predicting prostate biopsy outcomes has been well established for patients with prostate-specific antigen (PSA) values between 2 and 10 ng/mL. However, the performance of *phi* remains unknown in patients with PSA >10 ng/mL, the vast majority in Chinese biopsy patients. We aimed to assess the ability of *phi* to predict prostate cancer (PCa) and high-grade disease (Gleason Score >/=7) on biopsy in a Chinese population.

Methods:

This is a prospective, observational, multi-center study of consecutive patients who underwent a transrectal ultrasound guided prostate biopsy at four hospitals in Shanghai, China from August 2013 to December 2014.

Results:

In the cohort of 1538 patients, the detection rate of PCa was 40.2%. *phi* had a significantly better predictive performance for PCa than total PSA (tPSA). The areas under the receiver operating characteristic curve (AUC) were 0.90 and 0.79 for *phi* and tPSA, respectively, P<0.0001. A considerable proportion of patients in the cohort had PSAs >10 ng/mL (N=838, 54.5%). The detection rates of PCa were 35.9% and 57.7% in patients with tPSA 10.1–20 and 20.1–50 ng/mL, respectively.
The AUCs of *phi* (0.79 and 0.89, for these two groups, respectively) were also significantly higher than tPSA (0.57 and 0.63, respectively), both P<0.0001. If a *phi* </=35 was used as the cutoff, 599/1538 (39%) biopsies could have been avoided at a cost of missing small numbers of PCa patients: 49 (7.93%) PCa patients, including 18 (3.69%) high-grade tumors.

Conclusion:

Results from this study suggest that *phi* can be used to predict PCa and high-grade disease in Chinese men with high PSA levels (>10 ng/mL).

Asian Journal of Andrology. 2016; 18: 1-5.

Prospective validation of %p2PSA and the Prostate Health Index, in prostate cancer detection in initial prostate biopsies of Asian men, with total PSA 4–10 ng ml^{-1}.

Authors: Tan LG, Tan YK, Tai BC, et al.

Background:

Despite its widespread use for prostate cancer screening, low specificity makes PSA a suboptimal biomarker, especially in the diagnostic 'gray zone' of 4–10 ng/ml^{-1}. False positives lead to unnecessary biopsies with attendant morbidities.

Methods:

This is the first prospective validation study of %p2PSA and the Prostate Health Index *(phi)* in Asian men presenting with a total PSA between 4.0 and 10 ng/ml^{-1}. We studied 157 Asian men between 50 and 75 years old, with normal per rectal prostate examinations, undergoing their first prostate biopsy, using a standardized biopsy protocol for PSA levels of 4–10 ng/ml^{-1}.

Results:

Thirty (19.1%) were found to have prostate cancer on biopsy. Statistically significant differences between patients with and without prostate cancer were found for total PSA, p2PSA, %p2PSA and *phi*.

The areas under the curve of the receiver operating characteristic curve for total PSA, %fPSA, %p2PSA and *phi* were 0.479, 0.420, 0.695, and 0.794, respectively.

Conclusions:

phi predicts prostatic biopsies results best. At a sensitivity of 90%, the specificity (95% CI) of *phi* was 58.3%, more than triple the specificity of total PSA at 17.3%, potentially avoiding 77 (49%) unnecessary biopsies. Similar to studies in mainly Caucasian populations, we have prospectively shown that %p2PSA and *phi* greatly outperform total and free to total PSA ratio, in the detection of prostate cancer at first biopsy. Higher *phi* levels also correspond to increasing the risk of detecting GS≥7 cancers. We have validated the use of *phi* to aid decision making regarding prostate biopsies in Asian men with serum PSA between 4 and 10 ng ml^{-1}.

European Urology. 2014; 66(5): 906-12.

Multicenter European external validation of a Prostate Health Index–based nomogram for predicting prostate cancer at extended biopsy.

Authors: Lughezzani G, Lazzeri M, Haese A, et al.

Objective:

To externally validate a previously developed Prostate Health Index *(phi)*–based nomogram for predicting the presence of prostate cancer (PCa) at biopsy.

Design, setting and participants:

The study population consisted of 883 patients who were scheduled for a prostate biopsy at one of five European tertiary care centers. Total prostate-specific antigen (tPSA), free prostate-specific antigen (fPSA), and [−2]pro–prostate-specific antigen (p2PSA) levels were determined. The fPSA-to-tPSA ratio (%fPSA), p2PSA, and *phi* ([p2PSA/fPSA]×√tPSA) were calculated.

Results and limitations:

Of 833 patients, 365 (41.3%) were diagnosed with PCa at extended prostate biopsy. In accuracy analyses, *phi* was the most informative predictor of PCa (0.68), outperforming tPSA (0.51) and %fPSA (0.64).

The predictive accuracy of the previously developed nomogram was 75.2% (95% confidence interval, 71.4–78.1). Calibration of the nomogram was good in patients at a low to intermediate predicted probability of PCa, while calibration was suboptimal, with a tendency to overestimate the presence of PCa, in high-risk patients. Finally, DCA demonstrated that the use of the *phi*-based nomogram resulted in the highest net benefit. The main limitation of the study is the fact that only Caucasian patients were included.

Conclusions:

At external validation, the previously developed *phi*-based nomogram confirmed its ability to determine the presence of PCa at biopsy. These findings provide further evidence supporting the potential role of the nomogram in the biopsy decision pathway for European men with suspected PCa.

Patient summary:

In the current study, we externally validated a Prostate Health Index–based nomogram to predict the presence of prostate cancer (PCa) at biopsy. This tool may help clinicians determine the need for a prostate biopsy in European patients with suspected PCa.

Urology. 2014; 83(3): 606-12.

Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [-2]proPSA (p2PSA), %p2PSA, and Prostate Health Index in men with a total prostate-specific antigen of 4–10 ng/ml and normal digital rectal examination.

Authors: Lazzeri M, Abrate A, Lughezzani G, et al.

Objectives:

To investigate the relationship between serum [-2]proPSA (p2PSA) and derivatives with chronic histologic prostatic inflammation (CHPI) in men undergoing prostate biopsy for suspected prostate cancer (PCa).

Methods:

This nested case-control study resulted from an observational prospective trial for the definition of sensibility, specificity and accuracy of p2PSA, %p2PSA and Beckman Coulter Prostate Health Index *(phi)*, in men undergoing prostate biopsy, with a total prostate-specific antigen (PSA) of 4–10 ng/mL and normal digital rectal examination. CHPI was the outcome of interest and defined as the presence of moderate to large infiltration of lymphomononuclear cells with interstitial and/or glandular disruption in absence of PCa. p2PSA, %p2PSA and *phi* were considered the index tests and compared with the established biomarker reference standard tests: tPSA, fPSA and %fPSA.

Results:

Of 267 patients subjected to prostate biopsy, 73 (27.3%) patients were diagnosed with CHPI. Comparing CHPI with PCa patients, %p2PSA and *phi* were found to be significantly lower, whereas fPSA and %fPSA were significantly higher. %p2PSA and *phi* were the most accurate predictors of CHPI at biopsy, significantly outperforming tPSA, fPSA and %fPSA. On the contrary, no significant differences were found in PSA, p2PSA, and derivatives between CHPI and benign prostatic hyperplasia (BPH) patients.

Conclusion:

Our findings showed that p2PSA, %p2PSA and *phi* values might discriminate PCa from CHPI or BPH, but not CHPI from BPH, in men with a total PSA 4–10 ng/mL and normal digital rectal examination. p2PSA isoform and its derivatives could be useful in clinical decision making to avoid unnecessary biopsies in patients with CHPI and elevated tPSA value.

"*phi* reliably identifies the remaining clinically significant tumors in men with a Prostate Imaging Reporting and Data System (PIRADS) score <3."

— Loeb S. European urology 2017;72:654-5

Oncotarget 8(45): 79279-79288.

The Prostate Health Index *(phi)* predicts oncological outcome and biochemical recurrence after radical prostatectomy — analysis in 437 patients.

Authors: Maxeiner, A., E. Kilic, et al. (2017)

Purpose:

To investigate the Prostate-Health-Index *(phi)* for pathological outcome prediction following radical prostatectomy and also for biochemical recurrence prediction in comparison to established parameters such as Gleason-score, pathological tumor stage, resection status (R0/1) and prostate-specific antigen (PSA).

Methods:

Out of a cohort of 460 cases with preoperative *phi*-measurements (World Health Organization calibration: Beckman Coulter Access-2-Immunoassay) between 2001 and 2014, 437 patients with complete follow up data were included.

Results:

From these 437 patients, 87 (19.9%) developed a biochemical recurrence. Patient characteristics were compared by using chi-square test. Predictors were analyzed by multivariate adjusted logistic and Cox regression. The median follow up for a biochemical recurrence was 65 (range 3–161) months. *phi*, PSA, [-2]proPSA, *phi*- and PSA-density performed as significant variables ($p<0.05$) for cancer aggressiveness: Gleason-score <7 or >/=7 (ISUP grade 1 or >/=2) . Concerning pathological tumor stage discrimination and prediction, variables as *phi*, PSA, %fPSA, [-2]proPSA, *phi*- and PSA-density significantly discriminated between stages <pT3 and >/=pT3 with the highest AUC (0.7) for *phi*. In biochemical recurrence prediction *phi*, PSA, [-2]proPSA, *phi*- and PSA-density were the strongest predictors.

Conclusions:

Due to heterogeneity of time spans to biochemical recurrence, longer follow up periods are crucial. This study with a median follow up of more than 5 years, confirmed a clinical value for *phi* as an independent biomarker essential for biochemical recurrence prediction.

"*phi* adds predictive performance to image-guided detection of clinically significant cancers and has particular value in determining re-biopsy need in men with a negative mpMRI."

— Gnanapragasam V.J. Scientific Report 2016; 6: 35364

"The 4K panel and *phi* similarly improved discrimination when predicting PCa and high-grade PCa."

— Nordström T, et al. 2015 European Urology.

Value in Health. 2016;19(2):153-57.

The cost-effectiveness of prostate cancer detection with the use of Prostate Health Index.

Authors: Heijinsdijk EAM, Denham D, de Kong HJ.

Background:

Clinical trial results suggested that prostate-specific antigen (PSA) screening can reduce prostate cancer mortality. Nevertheless, because the specificity of the PSA test for cancer detection is low, it leads to many negative biopsies. The Beckman Coulter Prostate Health Index *(phi)* testing demonstrates improved specificity compared with the PSA-only screening and therefore may improve the cost-effectiveness of prostate cancer detection.

Objectives:

To examine the cost-effectiveness of adding *phi* testing to improve cancer detection for men with elevated serum PSA.

Methods:

A microsimulation model, based on the results of the European Randomized Study of Screening for Prostate Cancer trial, was used to evaluate the effects of PSA screening and *phi* reflex testing. We predicted the numbers of prostate cancers, negative biopsies, deaths, quality-adjusted life-years gained and cost-effectiveness of both PSA (cutoff 3 ng/mL) and *phi* (cutoff 25) testing methods for a European population, screened from age 50 to 75 years at 4-year intervals.

Results:

When the *phi* test was added to the PSA screening, for men with a PSA between 3 and 10 ng/mL, the model predicted a 23% reduction in negative biopsies. This would lead to a 17% reduction in costs for diagnostics and 1% reduction in total costs for prostate cancer. The cost-effectiveness (3.5% discounted) was 11% better. Limitations found were the modeling assumptions on the sensitivity and specificity of *phi* by tumor stage and cutoff values.

Conclusions:

Compared with PSA-only screening, the use of a *phi* test can substantially reduce the number of negative biopsies and improve the cost-effectiveness of prostate cancer detection.

Prostate Cancer Prostatic Dis.

Clinical utility of the Prostate Health Index *(phi)* for biopsy decision management in a large group urology practice setting.

Authors: White, J., B. V. Shenoy, et al. (2017)

Background:

Deciding when to biopsy a man with non-suspicious DRE findings and tPSA in the 4–10 ng/ml range can be challenging, because two-thirds of such biopsies are typically found to be benign. The Prostate Health Index (*phi*) exhibits significantly improved diagnostic accuracy for prostate cancer detection when compared to tPSA and %fPSA, however only one published study to date has investigated its impact on biopsy decisions in clinical practice.

Methods:

An IRB approved observational study was conducted at four large urology group practices using a physician reported two-part questionnaire. Physician recommendations were recorded before and after receiving the *phi* test result. A historical control group was queried from each site's electronic medical records for eligible men who were seen by the same participating urologists prior to the implementation of the *phi* test in their practice. 506 men receiving a *phi* test were prospectively enrolled and 683 men were identified for the historical control group (without *phi*). Biopsy and pathological findings were also recorded for both groups.

Results:

Men receiving a *phi* test showed a significant reduction in biopsy procedures performed when compared to the historical control group (36.4% vs. 60.3%, respectively, P<0.0001). Based on questionnaire responses, the *phi* score impacted the physician's patient management plan in 73% of cases, including biopsy deferrals when the *phi* score was low, and decisions to perform biopsies when the *phi* score indicated an intermediate or high probability of prostate cancer (*phi*>/=36).

Conclusions:

phi testing significantly impacted the physician's biopsy decision for men with tPSA in the 4–10 ng/ml range and non-suspicious DRE findings. Appropriate utilization of *phi* resulted in a significant reduction in biopsy procedures performed compared to historical patients seen by the same participating urologists who would have met enrollment eligibility but did not receive a *phi* test.

To learn more about *phi*, **please visit http://prostatehealthindex.us/**

"We demonstrated that preoperative *phi* levels may help to determine the probability of developing BCR in both the preoperative and the postoperative settings."

— Lughezzani G, et al. 2015 Urologic Oncology

Clin Genitourin Cancer 15(4): 429-439 e421.

A systematic review and meta-analysis of the diagnostic accuracy of Prostate Health Index and 4-kallikrein panel score in predicting overall and high-grade prostate cancer.

Authors: Russo, G. I., F. Regis, et al. (2017)

Objectives:

Markers for prostate cancer (PCa) have progressed over recent years. In particular, the Prostate Health Index *(phi)* and the 4-kallikrein (4K) panel have been demonstrated to improve the diagnosis of PCa. We aimed to review the diagnostic accuracy of *phi* and the 4K panel for PCa detection.

Patients and methods:

We performed a systematic literature search of PubMed, EMBASE, Cochrane, and Academic One File databases until July 2016. We included diagnostic accuracy studies that used *phi* or 4K panel for the diagnosis of PCa or high-grade PCa. The methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

Results:

Twenty-eight studies including 16,762 patients have been included for the analysis. The pooled data showed a sensitivity of 0.89 and 0.74 for *phi* and 4K panel, respectively, for PCa detection and a pooled specificity of 0.34 and 0.60 for *phi* and 4K panel, respectively. The derived area under the curve (AUC) from the hierarchical summary receiver operating characteristic (HSROC) showed an accuracy of 0.76 and 0.72 for *phi* and 4K panel respectively. For high-grade PCa detection, the pooled sensitivity was 0.93 and 0.87 for *phi* and 4K panel, respectively, whereas the pooled specificity was 0.34 and 0.61 for *phi* and 4K panel, respectively. The derived AUC from the HSROC showed an accuracy of 0.82 and 0.81 for *phi* and 4K panel, respectively. Both *phi* and the 4K panel provided good diagnostic accuracy in detecting overall and high-grade PCa.

Urologic Oncology: Seminars and Original Investigations. 2015; 33(4): 163.e15-23.

Prognostic accuracy of Prostate Health Index and urinary prostate cancer antigen 3 in predicting pathologic features after radical prostatectomy.

Authors: Cantiello F, Russo GI, Ferro M, et al.

Objectives:

To compare the prognostic accuracy of Prostate Health Index *(phi)* and prostate cancer antigen 3 in predicting pathologic features in a cohort of patients who underwent radical prostatectomy (RP) for prostate cancer (PCa).

Methods and materials:

We evaluated 156 patients with biopsy-proven, clinically localized PCa who underwent RP between January 2013 and December 2013 at 2 tertiary care institutions. Blood and urinary specimens were collected before initial prostate biopsy for [-2] pro–prostate-specific antigen (PSA), its derivates, and PCA3 measurements. Univariate and multivariate logistic regression analyses were carried out to determine the variables that were potentially predictive of tumor volume >0.5 ml, pathologic Gleason sum ≥7, pathologically confirmed significant PCa, extracapsular extension and seminal vesicles invasions.

Results:

On multivariate analyses and after bootstrapping with 1,000 resampled data, the inclusion of *phi* significantly increased the accuracy of a baseline multivariate model, which included patient age, total PSA, free PSA, rate of positive cores, clinical stage, prostate volume, body mass index and biopsy Gleason score (GS), in predicting the study outcomes. Particularly, to predict tumor volume >0.5, the addition of *phi* to the baseline model significantly increased predictive accuracy by 7.9% (area under the receiver-operating characteristics curve [AUC]=89.3 vs. 97.2, P>0.05), whereas PCA3 did not lead to a significant increase.

Although both *phi* and PCA3 significantly improved predictive accuracy to predict extracapsular extension compared with the baseline model, achieving independent predictor status (all P's <0.01), only *phi* led to a significant improvement in the prediction of seminal vesicles invasions (AUC=92.2, P<0.05 with a gain of 3.6%).

In the subset of patients with GS≤6, *phi* significantly improved predictive accuracy by 7.6% compared with the baseline model (AUC=89.7 vs. 97.3) to predict pathologically confirmed significant PCa and by 5.9% compared with the baseline model (AUC=83.1 vs. 89.0) to predict pathologic GS≥7. For these outcomes, PCA3 did not add incremental predictive value.

Conclusions:

In a cohort of patients who underwent RP, *phi* is significantly better than PCA3 in the ability to predict the presence of both more aggressive and extended PCa.

European Urology. 2015; 68(1): 139-46.

Comparison between the four-kallikrein panel and Prostate Health Index for predicting prostate cancer.

Authors: Nordström T, Vickers A, Assel M, et al.

Background:

The four-kallikrein panel and the Prostate Health Index *(phi)* have been shown to improve prediction of prostate cancer (PCa) compared with prostate-specific antigen (PSA). No comparison of the four-kallikrein panel and *phi* has been presented.

Objective:

To compare the four-kallikrein panel and *phi* for predicting PCa in an independent cohort.

Design, setting and participants:

Participants were from a population-based cohort of PSA-tested men in Stockholm County. We included 531 men with PSA levels between 3 and 15 ng/ml undergoing first-time prostate biopsy during 2010–2012.

Outcome measurements and statistical analysis:

Models were fitted to case status. We computed calibration curves, the area under the receiver-operating characteristics curve (AUC), decision curves and percentage of saved biopsies.

Results and limitations:

The four-kallikrein panel showed AUCs of 69.0 when predicting any-grade PCa and 71.8 when predicting high-grade cancer (Gleason score ≥7). Similar values were found for *phi*: 70.4 and 71.1, respectively. Both models had higher AUCs than a base model with PSA value and age (p<0.0001 for both); differences between models were not significant. Sensitivity analyses including men with any PSA level or a previous biopsy did not materially affect our findings. Using 10% predicted risk of high-grade PCa by the four-kallikrein panel or *phi* of 39 as cutoff for biopsy saved 29% of performed biopsies at a cost of delayed diagnosis for 10% of the men with high-grade cancers. Both models showed limited net benefit in decision analysis. The main study limitation was lack of digital rectal examination data and biopsy decision being based on PSA information.

Conclusions:

The four-kallikrein panel and *phi* similarly improved discrimination when predicting PCa and high-grade PCa. Both are simple blood tests that can reduce the number of unnecessary biopsies compared with screening with total PSA, representing an important new option to reduce harm.

Patient summary:

Prostate-specific antigen screening is controversial due to limitations of the test. We found that two blood tests, the Prostate Health Index and the four-kallikrein panel, performed similarly and could both aid in decision making among Swedish men undergoing a prostate biopsy.

Prostate Cancer Prostatic Dis 20(2): 228-233.

Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice.

Authors: Tosoian, J. J., S. C. Druskin, et al. (2017)

Background:

The Prostate Health Index *(phi)* outperforms PSA and other PSA derivatives for the diagnosis of prostate cancer (PCa). The impact of *phi* testing in the real-world clinical setting has not been previously assessed.

Methods:

In a single, large, academic center, *phi* was tested in 345 patients presenting for diagnostic evaluation for PCa. Findings on prostate biopsy (including Grade Group (GG), defined as GG1: Gleason score (GS) 6, GG2: GS 3+4=7, GG3: GS 4+3=7, GG4: GS 8 and GG5: GS 9–10), magnetic resonance imaging (MRI) and radical prostatectomy (RP) were prospectively recorded. Biopsy rates and outcomes were compared with a contemporary cohort that did not undergo phi testing (n=1318).

Results:

Overall, 39% of men with *phi* testing underwent prostate biopsy. No men with *phi*<19.6 were diagnosed with PCa, and only three men with *phi*<27 had cancer of GG2. *phi* was superior to PSA for the prediction of any PCa (area under the receiver operating characteristic curve (AUC) 0.72 vs. 0.47) and GG2 PCa (AUC 0.77 vs. 0.53) on prostate biopsy. Among men undergoing MRI and phi, no men with *phi*<27 and PI-RADS3 had GG2 cancer. For those men proceeding to RP, increasing *phi* was associated with higher pathologic GG (P=0.002) and stage (P=0.001). Compared with patients who did not undergo *phi* testing, the use of *phi* was associated with a 9% reduction in the rate of prostate biopsy (39% vs. 48%; P<0.001). Importantly, the reduction in biopsy among the *phi* population was secondary to decreased incidence of negative (8%) and GG1 (1%) biopsies, whereas the proportion of biopsies detecting GG2 cancers remained unchanged.

Conclusions:

In this large, real-time clinical experience, *phi* outperformed PSA alone, was associated with high-grade PCa, and provided complementary information to MRI. Incorporation of *phi* into clinical practice reduced the rate of unnecessary biopsies without changing the frequency of detection of higher-grade cancers.

BJU Int.

Combining Prostate Health Index density, magnetic resonance imaging and prior negative biopsy status to improve the detection of clinically significant prostate cancer.

Authors: Druskin, S. C., J. J. Tosoian, et al. (2017)

Objectives:

To determine the performance of Prostate Health Index *(phi)* density (PHID) combined with MRI and prior negative biopsy (PNB) status for the diagnosis of clinically significant prostate cancer (PCa).

Patients and Methods:

Patients without a prior diagnosis of PCa, with elevated prostate-specific antigen and a normal digital rectal examination who underwent *phi* testing prospectively prior to prostate biopsy were included in this study. PHID was calculated retrospectively using prostate volume derived from transrectal ultrasonography at biopsy. Univariable and multivariable logistic regression modelling, along with receiver-operating characteristic (ROC) curve analysis, was used to determine the ability of serum biomarkers to predict clinically significant PCa (defined as either grade group [GG]>/=2 disease or GG1 PCa detected in >2 cores or >50% of any one core) on biopsy. Age, PNB status and Prostate Imaging Reporting and Data System (PI-RADS) score were incorporated into the regression models.

Results:

Of the 241 men who qualified for the study, 91 (37.8%) had clinically significant PCa on biopsy. The median (interquartile range) PHID was 0.74 (0.44–1.24); it was 1.18 (0.77–1.83) and 0.55 (0.38–0.89) in those with and without clinically significant PCa on biopsy, respectively (P<0.001). On univariable logistic regression, age and PNB status were associated with clinically significant cancer. Of the tested biomarkers, PHID demonstrated the highest discriminative ability for clinically significant disease (area under the ROC curve [AUC] 0.78 for the univariable model). That continued to be the case in multivariable logistic regression models incorporating age and PNB status (AUC 0.82). At a threshold of 0.44, representing the 25th percentile of PHID in the cohort, PHID was 92.3% sensitive and 35.3% specific for clinically significant PCa; the sensitivity and specificity were 93.0% and 32.4% and 97.4% and 29.1% for GG>/=2 and GG>/=3 disease, respectively. In the 104 men who underwent MRI, PI-RADS score was complementary to PHID, with a PI-RADS score >/=3 or, if PI-RADS score </=2, a PHID >/=0.44, detecting 100% of clinically significant disease. For that subgroup, of the biomarkers tested, PHID (AUC 0.90) demonstrated the highest discriminative ability for clinically significant disease on multivariable logistic regression incorporating age, PNB status and PI-RADS score.

Conclusions:

In this contemporary cohort of men undergoing prostate biopsy for the diagnosis of PCa, PHID outperformed PHI and other PSA derivatives in the diagnosis of clinically significant cancer. Incorporating age, PNB status and PI-RADS score led to even further gains in the diagnostic performance of PHID. Furthermore, PI-RADS score was found to be complementary to PHID. Using 0.44 as a threshold for PHID, 35.3% of unnecessary biopsies could have been avoided at the cost of missing 7.7% of clinically significant cancers. Despite these encouraging results, prospective validation is needed.

Sci Rep 6: 35364.

The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant prostate cancers in a repeat biopsy population.

Authors: TGnanapragasam, V. J., K. Burling, et al. (2016)

Background:

Both multi-parametric MRI (mpMRI) and the Prostate Health Index *(phi)* have shown promise in predicting a positive biopsy in men with suspected prostate cancer. Here we investigated the value of combining both tests in men requiring a repeat biopsy.

Methods:

phi scores were measured in men undergoing re-biopsy with an mpMRI image-guided transperineal approach (n=279, 94 with negative mpMRIs). The *phi* was assessed for ability to add value to mpMRI in predicting all or only significant cancers (Gleason>/=7). In this study adding *phi* to mpMRI improved overall and significant cancer prediction (AUC 0.71 and 0.75) compared to mpMRI + PSA alone (AUC 0.64 and 0.69 respectively).

Results:

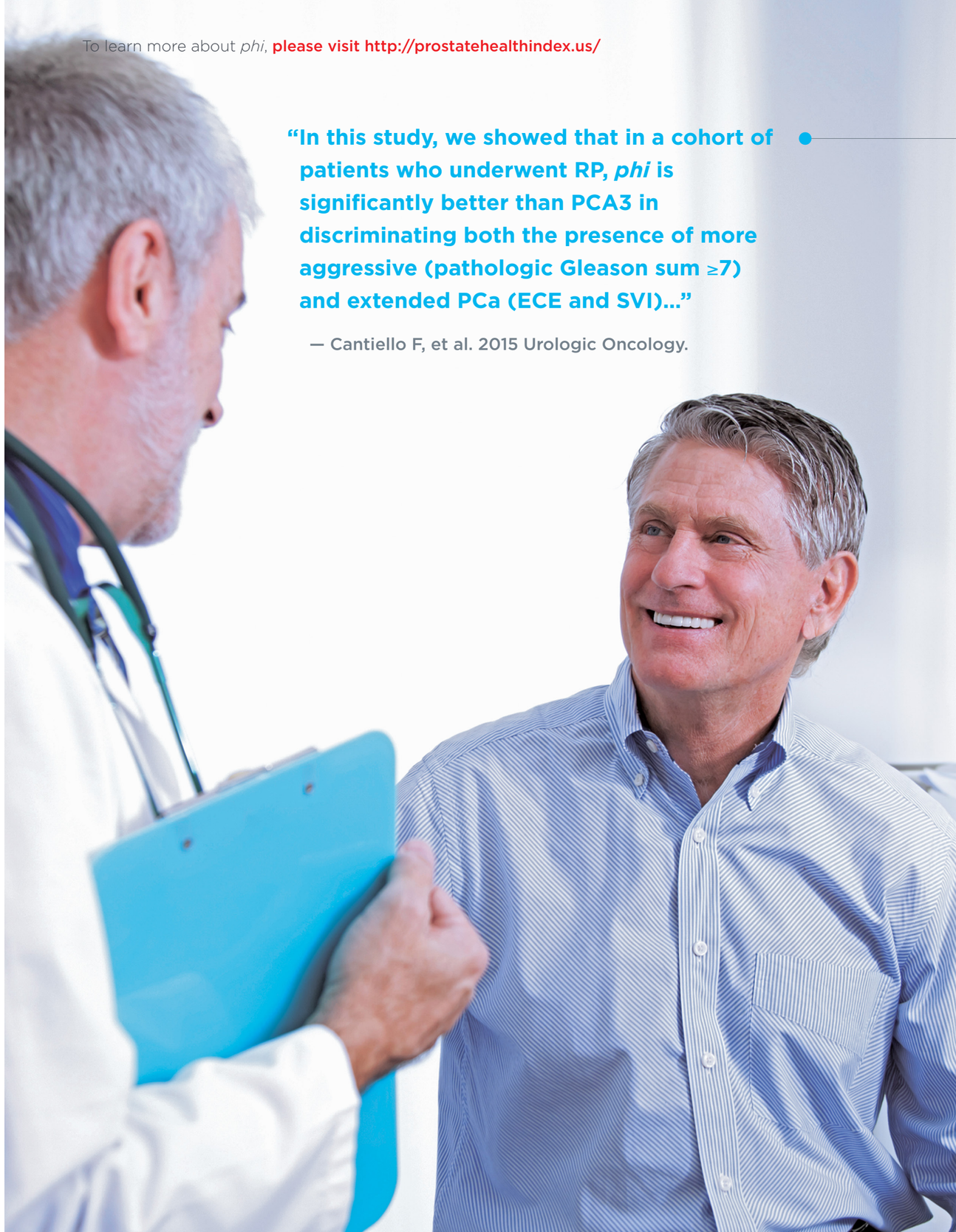
At a threshold of >/=35, *phi* + mpMRI demonstrated a NPV of 0.97 for excluding significant tumours. In mpMRI negative men, the *phi* again improved prediction of significant cancers; AUC 0.76 vs. 0.63 (mpMRI+PSA). Using a *phi*>/=35, only 1/21 significant cancers was missed and 31/73 (42%) men potentially spared a re-biopsy (NPV of 0.97, sensitivity 0.95). Decision curve analysis demonstrated clinically relevant utility of the PHI across threshold probabilities of 5–30%.

Conclusions:

The *phi* adds predictive performance to image-guided detection of clinically significant cancers and has particular value in determining re-biopsy need in men with a negative mpMRI.

"In this study, we showed that in a cohort of patients who underwent RP, *phi* is significantly better than PCA3 in discriminating both the presence of more aggressive (pathologic Gleason sum ≥7) and extended PCa (ECE and SVI)..."

— Cantiello F, et al. 2015 Urologic Oncology.



European Urology. 2015; 67(4): 619-26.

Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification.

Authors: Loeb S, Bruinsa SM, Nicholson J, et al.

Context:

Active surveillance (AS) is an important strategy to reduce prostate cancer overtreatment. However, the optimal criteria for eligibility and predictors of progression while on AS are debated.

Objective:

To review primary data on markers, genetic factors, and risk stratification for patient selection and predictors of progression during AS.

Evidence acquisition:

Electronic searches were conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to April 2014 for original articles on biomarkers and risk stratification for AS.

Evidence synthesis:

Patient factors associated with AS outcomes in some studies include age, race and family history. Multiple studies provide consistent evidence that a lower percentage of free prostate-specific antigen (PSA), a higher Prostate Health Index *(phi)*, a higher PSA density (PSAD), and greater biopsy core involvement at baseline predict a greater risk of progression. During follow-up, serial measurements of *phi* and PSAD, as well as repeat biopsy results, predict later biopsy progression. While some studies have suggested a univariate relationship between urinary prostate cancer antigen 3 (PCA3) and transmembrane protease, serine 2–v-ets avian erythroblastosis virus E26 oncogene homolog gene fusion (TMPRSS2:ERG) with adverse biopsy features, these markers have not been consistently shown to independently predict AS outcomes. No conclusive data support the use of genetic tests in AS. Limitations of these studies include heterogeneous definitions of progression and limited follow-up.

Conclusions:

There is a growing body of literature on patient characteristics, biopsy features, and biomarkers with potential utility in AS. More data are needed on practical applications such as combining these tests into multivariable clinical algorithms and long-term outcomes to further improve AS in the future.

Patient summary:

Several PSA–based tests (free PSA, *phi*, PSAD) and the extent of cancer on biopsy can help to stratify the risk of progression during active surveillance. Investigation of several other markers is under way.

J Cancer Res Clin Oncol. 2014; 140: 257–263.

The impact of baseline [−2]proPSA related indices on the prediction of pathological reclassification at 1 year during active surveillance for low risk prostate cancer: the Japanese multicenter study cohort.

Authors: Hirama H, Sugimoto M, Ito Kazuto.

Purpose:

Active surveillance (AS) is one potential solution to avoiding the overtreatment of favorable prostate cancer. By handling the AS strategy more safely, tumor aggressiveness may be evaluated more accurately. The aim of the present study was to evaluate the predictive impact of baseline prostate-specific antigen (PSA) isoform [−2]proPSA (p2PSA)-related indices on the pathological reclassification at 1 year during an AS program.

Methods:

Between 2002 and 2003, 134 males diagnosed with low-risk prostate cancer were registered in the Japanese multicenter study cohort as candidates for AS, and 118 (88 %) males actually proceeded to AS. Of the 118 patients, the 67 that underwent protocol biopsy at 1 year after beginning AS were enrolled in the present study. The predictive significance of various baseline clinicopathological features and p2PSA-related indices on pathological reclassification at 1 year after beginning AS were investigated.

Results:

The pathological reclassification rate was 37.3 %. According to the univariate analysis, prostate volume (p=0.049), number of biopsy cores (p=0.047), percentage of positive biopsy cores (p=0.023), p2PSA to free PSA ratio (%p2PSA) (p=0.003) and Prostate Health Index *(phi)* (p=0.010) at baseline were significantly different between the reclassification and non-reclassification groups. By multivariate logistic regression analysis, baseline %p2PSA (p = 0.008) and *phi* (p=0.008) were the only independent predictive factors for pathological upgrade at 1 year after AS commencement.

Conclusions:

Baseline %p2PSA and *phi* may predict the pathological reclassification at 1 year after starting AS, which could be due to the under detection of clinically significant prostate cancer at AS enrollment.

World Journal of Urology. 2015 July 21: 1-9.

phi and PCA3 improve the prognostic performance of PRIAS and Epstein criteria in predicting insignificant prostate cancer in men eligible for active surveillance.

Authors: Cantiello F, Russo GI, Cicione A, et al.

Purpose:

To assess the performance of Prostate Health Index *(phi)* and prostate cancer antigen 3 (PCA3) when added to the PRIAS or Epstein criteria in predicting the presence of pathologically insignificant prostate cancer (IPCa) in patients who underwent radical prostatectomy (RP) but were eligible for active surveillance (AS).

Methods:

An observational retrospective study was performed in 188 PCa patients treated with laparoscopic or robot-assisted RP but who were eligible for AS according to Epstein or PRIAS criteria. Blood and urinary specimens were collected before initial prostate biopsy for *phi* and PCA3 measurements. Multivariate logistic regression analyses and decision curve analysis were carried out to identify predictors of IPCa using the updated ERSPC definition.

Results:

At the multivariate analyses, the inclusion of both PCA3 and *phi* significantly increased the accuracy of the Epstein multivariate model in predicting IPCa with an increase of 17% (AUC=0.77) and of 32% (AUC=0.92), respectively. The inclusion of both PCA3 and *phi* also increased the predictive accuracy of the PRIAS multivariate model with an increase of 29% (AUC=0.87) and of 39% (AUC=0.97), respectively. DCA revealed that the multivariable models with the addition of *phi* or PCA3 showed a greater net benefit and performed better than the reference models. In a direct comparison, *phi* outperformed PCA3 performance resulting in higher net benefit.

Conclusions:

In a same cohort of patients eligible for AS, the addition of *phi* and PCA3 to Epstein or PRIAS models improved their prognostic performance. *phi* resulted in greater net benefit in predicting IPCa compared to PCA3.

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