THE PROSTATE HEALTH INDEX *(phi)* CLINICAL SUMMARY

Superior Performance Demonstrated through Multiple Peer-reviewed Publications

Prostate cancer continues to be a leading cause of cancer mortality in men. The American Cancer Society estimates that approximately 220,800 new cases will be diagnosed and 27,540 men will die from prostate cancer in 2015 in the United States. Approximately 1 man in 7 will be diagnosed with prostate cancer during his lifetime.[1]

Early detection of prostate cancer is an important health care issue. The PSA test is the standard prostate cancer screening test administered by primary care physicians and urologists around the world. However, approximately 75% of prostate biopsies performed are negative for cancer, which calls out the need for a more specific test to help reduce unnecessary biopsies. The Prostate Health Index *(phi)* provides more accurate information that physicians require for better decision-making. If a patient has an elevated PSA test result in the 4-10 ng/mL range, this simple blood test is an option to determine their risk of prostate cancer and whether or not a biopsy is warranted.

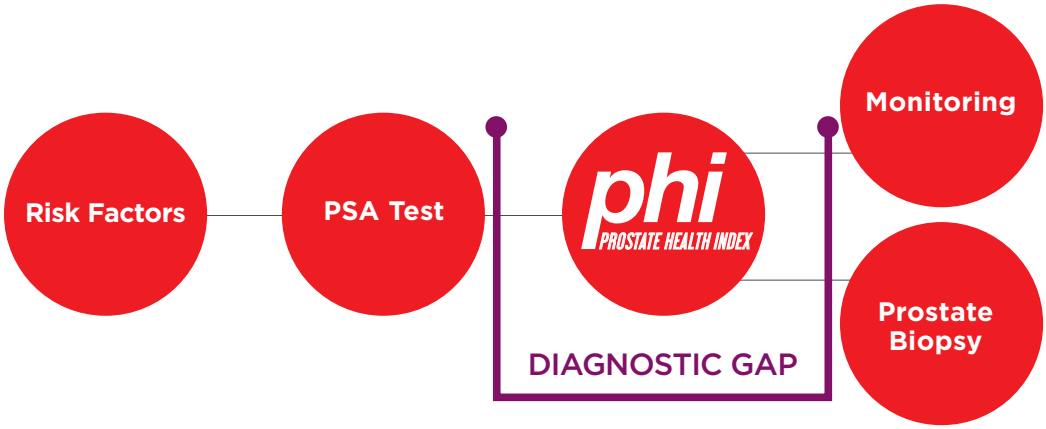
The *phi* test utilizes a calculation that combines the results of three quantitative blood serum immunoassays (PSA, free PSA and p2PSA) into a single numerical result (the "*phi* score"). This score gives you more accurate information about what an elevated PSA level might mean and the probability of finding prostate cancer with a biopsy. The new and novel p2PSA assay is specific to measuring [-2]proPSA. The [-2] proPSA biomarker is an isoform of free PSA that was identified as the most prostate cancer-specific form found in tumor extracts.[2]

BECKMAN COULTER

The Prostate Health Index: Filling the Diagnostic Gap

Results of the multi-center pivotal clinical trial showed that Beckman Coulter *phi* values significantly enhanced the clinical specificity for prostate cancer detection in men with PSA in the the 4 to 10 ng/mL PSA range.[3] A Beckman Coulter *phi* value of 27.0 corresponds to 90% clinical sensitivity and 31.1% clinical specificity. Therefore, nearly **1 in 3 men may avoid prostate biopsy** while detecting 90% of cancers if their Beckman Coulter *phi* value is less than 27.0[4].

Over 80 published clinical papers and meeting abstracts have demonstrated the benefits and economic value of the Prostate Health Index. These studies confirm that *phi* significantly improves clinical specificity for prostate cancer detection relative to PSA alone.



***phi* fills the diagnostic gap between PSA screening and a prostate biopsy. Combined with family and patient history, the *phi* score can be used to determine the best individualized patient management decisions.**

phi Peer-reviewed Publication Summary

The Prostate Health Index: Its Utility in Prostate Cancer Detection

Publication/Authors:

Urology Clinics of North America 2016: 43:1–6
Lepor A, Catalona WJ, Loeb S

Study Overview/Objective:

This article reviews the major studies on *phi* in prostate cancer detection and risk stratification.

Key Points:

- The Prostate Health Index (*phi*) addresses many of the drawbacks associated with PSA screening
- The specificity of *phi* is greater because *phi* is a combination of three different isoforms of PSA: total PSA, free PSA, and [-2]proPSA
- The Prostate Health Index is a simple blood test, but it outperforms any of its individual components for the identification of clinically significant prostate cancer
- The *phi* test is more specific for the detection of clinically significant prostate cancer than free and/or total PSA
- Increasing *phi* scores predict a greater risk of high-risk pathology and biochemical recurrence after radical prostatectomy
- The *phi* test performed at the initiation and during the course of active surveillance predicts subsequent biopsy reclassification

Article Conclusion:

Numerous large, prospective studies from geogra*phi*cally diverse regions have consistently demonstrated that *phi* is more specific for prostate cancer detection than existing standard reference tests of total and free PSA. Increasing *phi* scores predict a greater risk of clinically significant disease on biopsy and adverse prostatectomy outcomes.

phi Peer-reviewed Publication Summary

Serum Marker %[-2]proPSA and the Prostate Health Index Improve Diagnostic Accuracy for Clinically Relevant Prostate Cancer

Publication/Authors:
Robert W. Veltri
BJU International, January 2016, 117(1): 12-13

Publication Overview:
This article was an Editor's Choice letter published in the British Journal of Urology International by Dr. Robert W. Veltri, at the Department of Urology, Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Key Point:

› A multi-center study by Boegemann et al. assessed 769 men aged ≤ 65 years at their initial and repeat prostate biopsy diagnoses and %[-2]proPSA and *phi* were shown to be the strongest predictors of biopsy outcome

Article Conclusion:
Currently, evaluation of high-risk cancer is often based on genomic knowledge and has ~70–75% accuracy to offer personalized treatment regimens. The study by Boegemann et al. achieved similar accuracy using *phi* and routine clinicopathological features to create models for prostate cancer detection and repeat biopsy decision-making. Clearly, a prostate cancer risk predictor containing the best biomarkers, including *phi*, will improve the accuracy in the management of patients on active surveillance.

The Prostate Health Index *(phi)* Selectively Identifies Clinically-Significant Prostate Cancer

Publication/Authors:

The Journal of Urology 2015; 193(4):1163-1169. Loeb S, Sanda MG, Broyles DL, Shin SS, Bangma CH, Wei JT, Partin AW, Klee GG, Slawin KM, Marks LS, van Schaik RHN, Chan DW, Sokoll LJ, Cruz AB, Mizrahi IA, Catalona WJ

Study Objective:

The authors investigated whether *phi* improves specificity for detecting clinically significant prostate cancer and can help reduce prostate cancer overdiagnosis.

Study Overview:

- From the multi-center prospective trial, 658 men aged 50 years or older were identified with PSA 4 to 10 ng/mL and normal digital rectal examination who underwent prostate biopsy
- In this population, the performance of PSA, % free PSA, p2PSA and *phi* were compared to predict biopsy results and, specifically, the presence of clinically-significant prostate cancer using multiple criteria

Key Points:

- Results showed that *phi* was significantly higher in men with Gleason 7 or greater and "Epstein significant" cancer
- On ROC analysis, *phi* had the highest AUC for overall cancer, Gleason 7 or greater and significant cancer (see table below)
- At the 90% sensitivity cut off 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 cancer compared to 21.7% using % free PSA

Test/Biomarker	AUC		
	Overall	Gleason ≥7	Significant Cancer
phi	0.708	0.707	0.698
% free PSA	0.648	0.661	0.654
p2PSA	0.550	0.558	0.550
PSA	0.516	0.551	0.549

Article Conclusion:

The *phi* test outperforms its individual components of total, free and p2PSA for the identification of clinically-significant prostate cancer. The Prostate Health Index may be useful as part of a multivariable approach to reduce prostate biopsies and over diagnosis.

phi Peer-reviewed Publication Summary

Clinical Performance of Serum [-2]proPSA Derivatives, %p2PSA and *phi* in the Detection and Management of Prostate Cancer

Publication/Authors:

American Journal of Clinical and Experimental Urology 2014, 2(4): 343-350
Huang Y, Sun T, Zhong W, Wu C

Study Overview/Objective:

A systematic review of the available scientific evidences was performed to evaluate the potentials of %p2PSA and *phi* in clinical application. The review was focused on their application in diagnosis and active surveillance.

Key Points Regarding p2PSA:

- In histological analyses, proPSA was differentially expressed in the peripheral zone while undetectable in the transition zone in most prostate specimens leading to the conclusion that proPSA appears to be a more cancer-specific form of PSA
- Amino acid sequencing of whole purified PSA, isolated and tissues, showed that the proPSA in peripheral zone cancer consisted mainly of [-2]proPSA (p2PSA) rather than other proPSA

Key Points Regarding *phi:*

- Increased *phi* levels were strongly associated with patients harboring more aggressive diseases
- Furthermore, *phi* demonstrated potential ability to identify the progress of low-risk localized cancer under active surveillance
- The *phi* test also showed potential association with probability of metastatic progression and biochemical recurrence after radical prostatectomy
- Studies showed that if phi was added to the current prostate cancer screening strategies, overall reductions in cost can be achieved due to the reduction in the total number of office visits, laboratory tests and unnecessary biopsies

Article Conclusion:

Studies suggest that *phi* enhances the accuracy of detection, reduces the number of unnecessary biopsies and helps predict the aggressiveness of prostate cancer when compared to total PSA and free PSA.

Additional *phi* Peer-reviewed Publications

2015

Loeb S, Bruinsma SM, Nicholson J, Briganti A, Pickles T, Kakehi Y, Carlsson SV, Roobol MJ. Active surveillance for prostate cancer: A systematic review of clinicopathologic variables and biomarkers for risk stratification. European Urology 2015, 67:619-626.

2014

NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection. Version 1.2014 (PROSD-3).

Loeb S, Catalona W. The Prostate Health Index: a new test for the detection of prostate cancer. Therapeutic Advances in Urology 2014; 6(2) 74-77.

Filella X, Foj L, Auge JP, Molina R, Alcover J. Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer. Clin Chem Lab Med 2014 Sep; 52(9):1347-55.

Heidegger H, Klocker H, Steiner E, Skradski V, Ladurner M, Pichler R, Schafer G, Horninger W, Bektic J. [-2]proPSA is an early marker for prostate cancer aggressiveness. Prostate Cancer and Prostatic Diseases 2014 Mar; 17(1):70-4.

Hirama H, Sugimoto M, Ito K, Shiraishi T, Kakehi Y. 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. J Cancer Res Clin Oncol 2014; 140:257-263.

Lazzeri M, Abrate A, Lughezzani G, Gadda GM, Freschi M, Mistretta F, Lista G, Fossati N, Larcher A, Kinzikeeva E, Buffi N, Dell'Acqua V, Bini V, Montorsi F, Guazzoni G. 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. Oncology 2014 Mar; 83(3):606-12.

Murphy DG, Ahlering T, Catalona WJ, Crowe H, Crowe J, Clarke N, Cooperberg M, Gillatt D, Gleave M, Loeb S, Roobol M, Sartor O, Pickles T, Wootten A, Walsh P, Costello A. The Melbourne Consensus Statement on the Early Detection of Prostate Cancer. BJU International 2014; 113: 186–188.

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Ferro M, Bruzzese D, Perdonà S, Marino A, Mazzarella C, Perruolo G, D'Esposito V, Cosimato V, Buonerba C, Di Lorenzo G, Musi G, De Cobelli O, Chun FK, Terracciano D. Prostate health index (*phi*) and prostate cancer antigen 3 (PCA3) significantly improve prostate cancer detection at initial biopsy in a total PSA range of 2-10 ng/ml. PLoS One 2013 Jul 4; 8(7):e67687.

Hori S, Blanchet JS, McLoughlin J. From prostate-specific (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. BJU International 2013 Oct; 112(6):717-28.

Ito K, Miyakubo M, Sekine Y, Koike H, Matsui H, Shibata Y, Suzuki K. Diagnostic significance of [-2]pro-PSA and prostate dimension-adjusted PSA-related indices in men with total PSA in the 2.0-10.0 ng/mL range. World J Urol. 2013 Apr; 31(2):305-11.

Lazzeri M, Haese A, Abrate A, de la Taille A, Redorta JP, McNicholas T, Lughezzani G, Lista G, Larcher A, Bini V, Cestari A, Buffi N, Graefen M, Bosset O, Corvoisier PL, Breda A, de la Torre P, Fowler L, Roux J, Guazzoni G. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (*PHI*), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU Int. 2013 Aug; 112(3):313-21.

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Lazzeri M, Briganti A, Scattoni V, Lughezzani G, Larcher A, Gadda G, Lista G, Cestari A, Buffi N, Bini V, Freschi M, Rigatti P, Montorsi F, Guazzoni G. Serum index test %[-2]proPSA and Prostate Health Index are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy. J Urology 2012; 188: 1137-1143.

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Zhang M, Lu Y. From pro-prostate specific antigen, [-2]pro-prostate specific antigen to Beckman Coulter *phi*: the evolution of new biomarkers for early detection of prostatic carcinoma. Chin Med J 2012; 125(9): 1643-1649.

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4. p2PSA IFU

For Beckman Coulter's worldwide office locations and phone numbers, please visit www.beckmancoulter.com/contact

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