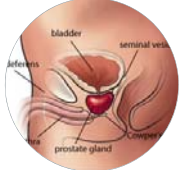




PROSTATE CANCER

- > In 2015, approx. 220,800 new cases of Prostate Cancer (Pca)
- > In 2015, approx. 27,540 deaths from PCa
- > 1 in 7 men will be diagnosed in his lifetime
- > 6 in 10 cases are diagnosed in men 65 or older
- > PCa is the 2nd leading cause of cancer death in men
- > Detection – Digital Rectal Exam (DRE) and Prostate-specific antigen (PSA) testing
- > Diagnosis- Biopsy and Transrectal Ultrasound (TRUS)

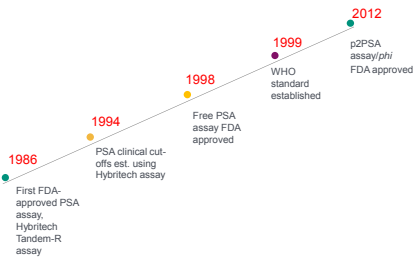


Prostate gland: small, walnut-shaped gland that produces seminal fluid for the nourishment and transport of sperm

www.cancer.org

© 2018 Beckman Coulter. All rights reserved. **More Intuitive. Easier.** **BECKMAN COULTER**

BECKMAN COULTER'S COMMITMENT TO PROSTATE DISEASE



- 1986**: First FDA-approved PSA assay, Hybritech Tandem-R assay
- 1994**: PSA clinical cut-offs est. using Hybritech assay
- 1998**: Free PSA assay FDA approved
- 1999**: WHO standard established
- 2012**: p2PSA assay/phi FDA approved

© 2018 Beckman Coulter. All rights reserved. **More Intuitive. Easier.** **BECKMAN COULTER**



PROSTATE CANCER SCREENING & THE PSA DEBATE

© 2018 Beckman Coulter. All rights reserved. **More Intuitive. Easier.** **BECKMAN COULTER**

PSA LIMITATIONS & CONTROVERSY

- › Elevated PSA may not indicate cancer
- › Even if cancer is present, elevated PSA may not indicate clinically significant cancer
- › Low specificity results in high costs
- › Result: Prostate cancer is over diagnosed and over treated
- › How can we make PSA a better marker?

© 2018 Beckman Coulter. All rights reserved.



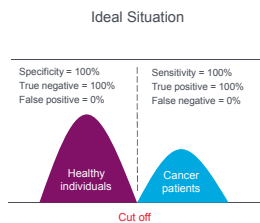
PROSTATE CANCER MARKERS:
OPTIMAL CHARACTERISTICS

- › Specificity
 - › Must be able to differentiate cancerous from normal prostate
 - › Separate prostate cancer from other cancers and disease types (e.g., BPH, prostatitis)
 - › "Tumor Specific"
 - › Ideally be able to differentiate aggressive from indolent cancers
- › Sensitivity
 - › Identify all individuals with prostate cancer
 - › Early marker of disease
- › Easily Detectable with Non-Invasive Methods

© 2018 Beckman Coulter. All rights reserved.



SENSITIVITY/SPECIFICITY



© 2018 Beckman Coulter. All rights reserved.



SENSITIVITY/SPECIFICITY

We choose a cut-off that provides the best balance of sensitivity and specificity

© 2018 Beckman Coulter. All rights reserved.

SENSITIVITY/SPECIFICITY OF TOTAL PSA

© 2018 Beckman Coulter. All rights reserved.

HYBRITECH PSA

As PSA levels increase, so does the probability of detecting cancer:

PSA (Hybritech Calibration)	PSA (WHO Calibration)	Probability of Cancer
0-2 ng/mL	0-3.1 ng/mL	13%
2-4 ng/mL	1.6-3.1 ng/mL	15%
4-10 ng/mL	3.1-7.8 ng/mL	25%
> 10 ng/mL	> 7.8 ng/mL	> 50%

- PSA concentrations are not definitive evidence for the presence or absence of prostate cancer.
- PSA testing should be done in conjunction with DRE, because PSA and DRE together provide the best aid in detecting prostate cancer.
- Note: biopsy is required to diagnose prostate cancer.

© 2018 Beckman Coulter. All rights reserved.

**GETTING MORE OUT OF PSA:
HOW CAN WE INCREASE ITS SPECIFICITY?**

HYBRITECH FREE PSA

- › Enhancing PSA clinical performance
 - › Up to 16% of new prostate cancer patients have a normal total PSA value (<4 ng/mL)
 - › About 75% of men with a PSA value of >4 ng/mL have benign histology on biopsy
- › Percent (%) free PSA
 - › Aids in the differentiation between cancer and benign conditions when the total PSA is between 4-10 ng/mL and DRE is negative
 - › Lower % free PSA values = higher risk of cancer
 - › Detection of most prostatic cancer cases (95% sensitivity)
 - › Up to 20% reduction in biopsies (20% specificity)
 - › Biopsy recommended when % free PSA is <25%
 - › Biopsies avoided in low cancer risk group

© 2018 Beckman Coulter. All rights reserved.



HYBRITECH FREE PSA

Probability of cancer based on PSA and % fPSA results (men with non-suspicious DRE results, any age):

PSA	Probability of Cancer	%fPSA	Probability of Cancer
0-2 ng/mL	1%	0-10%	56%
2-4 ng/mL	15%	10-15%	28%
4-10 ng/mL	25%	15-20%	20%
>10 ng/mL	>50%	20-25%	16%
		>25%	8%

› % fPSA can stratify risk for men with PSA between 4 and 10 ng/mL

© 2018 Beckman Coulter. All rights reserved.



PSA DEBATE

- › Negative consequences of over-diagnosis and over-treatment
- › False positives from PSA screening result in approximately 750,000 unnecessary biopsies per year in the United States
- › Hospitalization rates for infectious complications after biopsy range from 0.6% to 4.1%
- › Over 90% of the lowest-risk prostate cancer patients are still being treated radically in the U.S
- › However, it has been estimated that U.S. men presenting with metastatic disease would rise 300% if PSA testing was not performed
- › These are significant health-economic problems! A more specific test for prostate cancer is needed.

New England Journal of Medicine, 2016; 374 (18)

© 2018 Beckman Coulter. All rights reserved.



PSA TESTING: DOES IT HAVE A BENEFIT?

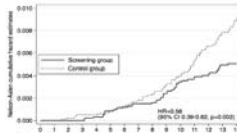
- › We can look at historical data for prostate cancer before and after the introduction of PSA testing:
- › Falling prostate cancer mortality rates
- › Falling advanced prostate cancer rates
- › Falling metastatic cancer rates

© 2018 Beckman Coulter. All rights reserved.



GÖTEBORG SCREENING TRIAL

- › Lower PC Mortality
- › 41% ↓ in advanced disease
- › >66% ↓ in men actually screened
- › 44% ↓ in PCa mortality
- › 56% ↓ in men actually screened
- › Despite the fact that 33% were managed with active surveillance (45% originally chose AS)
- › 18 year data (EAU 2014): Need to diagnose 9 men to prevent 1 prostate cancer death



Lancet Oncol 2010; 11: 725-732

© 2018 Beckman Coulter. All rights reserved.



PSA DEBATE

- › USPSTF Recommendation
 - › In May 2012, The U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer for all men
 - › The USPSTF issued a statement indicating the need for "a better test and better treatment options"

(USPSTF = US Preventative Services Task Force)

© 2018 Beckman Coulter. All rights reserved.



PROSTATE CANCER DETECTION: CLINICAL DILEMMA

- › AUA statement on the USPSTF recommendation
- › "There is strong evidence that PSA testing saves lives."
- › "We have seen a 40% reduction in prostate cancer-specific mortality in the U.S. over the most recent 20 years of PSA-based screening."
- › "Models have suggested that more than 50% of this reduction is due to early detection."

(USPSTF = US Preventative Services Task Force)

© 2018 Beckman Coulter. All rights reserved.



AUA 2016 UPDATE:
USPSTF GUIDELINES CALLED INTO QUESTION

- › Almost 90% of men in the control group actually had received PSA testing
- › The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial results have therefore been misinterpreted
- › Prostate screening was "wrongly convicted" on the basis of results of the PLCO trial

New England Journal of Medicine, 2016; 374 (18)

© 2018 Beckman Coulter. All rights reserved.



USPSTF 2017 UPDATE

- › "The decision about whether to be screened for prostate cancer should be an individual one."
- › "The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)-based screening for prostate cancer."
- › "The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older."
- › "This recommendation applies to adult men in the general U.S. population without symptoms or a previous diagnosis of prostate cancer. It also applies to men at increased risk of death from prostate cancer due to race or family history of prostate cancer."
- › "This recommendation does not apply to the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer."

(USPSTF = US Preventative Services Task Force)

© 2018 Beckman Coulter. All rights reserved.



P2PSA & THE PROSTATE HEALTH INDEX

More Insights From **BECKMAN COULTER**

IN 2005, THE NATIONAL CANCER INSTITUTE FORMED THE EDNRN (THE EARLY DETECTION RESEARCH NETWORK), WHICH IS A GROUP OF INVESTIGATORS TO IDENTIFY AND VALIDATE NEW CANCER BIOMARKERS.

PSA

[-2]proPSA:
A new biomarker that is more specific for prostate cancer

© 2018 Beckman Coulter. All rights reserved. More Insights From **BECKMAN COULTER**

IN 2010, RESEARCH SHOWED PROMISING RESULTS.

Research Article

A Prospective, Multicenter, National Cancer Institute Early Detection Research Network Study of [-2]proPSA: Improving Prostate Cancer Detection and Correlating with Cancer Aggressiveness

Lei J. Bostof, Mark G. Sandt, Dong Peng, Josh Riggs, Sean A. Mucci, Dennis L. Brubaker, Alan W. Partin, Sundeep Srinivasan, Ian M. Thompson, Jim T. Wei, Zhen Zhang, and Daniel W. Chan

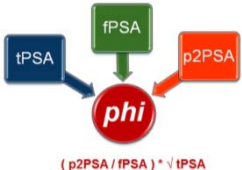
- > Independent investigators to identify & validate new cancer biomarkers
- > [-2] proPSA was the first!
- > Subjects
 - > 566 men, in a prospective PCa detection study at four National Cancer Institute Early Detection Research Network clinical validation centers
- > Inclusion criteria
 - > 40 years and older, no prior prostate surgery, biopsy or history of PCa, no use of 5- α reductase inhibitors, and at least a 10 core template biopsy (post-enrollment)
- > Results
 - > Calculated %[-2]proPSA ([-2]proPSA/free PSA) – found this had value
 - > In the 2 to 10 ng/mL PSA range, %[-2]proPSA outperformed %fPSA (AUC 0.76 vs. 0.66)

© 2018 Beckman Coulter. All rights reserved. More Insights From **BECKMAN COULTER**

BECKMAN COULTER'S PROSTATE HEALTH INDEX (*phi*)

What is *phi*?

> "*phi* score" is calculated based on the results of these 3 assays



> Due to its increased specificity, *phi* has the potential to reduce negative biopsies by 30 percent

> "*phi* score" is calculated based on the results of these 3 assays

> Indicates a patient's relative risk for developing prostate cancer

© 2018 Beckman Coulter. All rights reserved. [More Information Here](#)

US pivotal study

A Multicenter Study of [-2]Pro-Prostate Specific Antigen Combined With Prostate Specific Antigen and Free Prostate Specific Antigen for Prostate Cancer Detection in the 2.0 to 10.0 ng/ml Prostate Specific Antigen Range

William J. Catalona,*† Alan W. Partin,† Martin G. Sanda,† John T. Wei,† George G. Kline,† Chris H. Bangma, Kevin M. Slawin,† Leonard S. Marks, Stacy Lott, Dennis L. Broyles,† Sanghyuk S. Shin,† Amabelle B. Cruz,† Daniel W. Chan, Lon J. Sokoll, William L. Roberts,† Ron H. N. van Schick and Isaac A. Mizrahi

> **Subjects**

> 892 men with no history of prostate cancer, in a prospective multi-institutional trial

> **Inclusion criteria**

> ≥50y, Normal DRE, pre-study PSA 2.0–10 ng/mL and 6-core or greater prostate biopsy

> **Results**

> The AUC of *phi* exceeded PSA & fPSA

> *phi* = 0.724; fPSA = 0.670; PSA = 0.525

> Using *phi*=55 as cutoff: 4.7-fold increased risk of PCa and a 1.61-fold increased risk of a Gleason Score greater than or equal to 4+3=7 disease on biopsy

> Suggested a discrimination of indolent vs. aggressive cancers... higher *phi*, higher Gleason score

Reference: U.S. Pivotal Investigation J of Urology. 2011 185: 1650-1655.

© 2018 Beckman Coulter. All rights reserved. [More Information Here](#)

PHI CLINICAL STUDY PROTOCOL

US pivotal study

> The study investigated the following:

> Whether the use of *phi* improves specificity for detecting prostate cancer in the 4 to 10 ng/mL PSA range

> Whether *phi* improves the detection of prostate cancer relative to total PSA and %free PSA

> **Study Population & Inclusion Criteria**

> 658 men

> PSA between 4-10 ng/mL

> 50 years or older

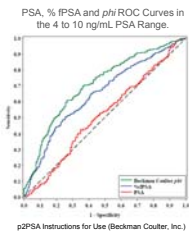
> Negative DRE

p2PSA Instructions for Use (REF B03704) Beckman Coulter, Inc.

© 2018 Beckman Coulter. All rights reserved. [More Information Here](#)

PHI CLINICAL STUDY RESULTS

- › At 90% sensitivity, the specificity of phi was 31.1% compared to 19.8% for % free PSA and 10.8% for PSA.
- › At phi cutoffs ranging from 27 to 55, the probability of cancer ranged from 9.8% to 50.1%.
- › Increasing phi values were also associated with biopsy Gleason score and significant cancer based on Epstein criteria.



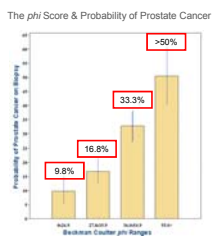
© 2018 Beckman Coulter. All rights reserved.



THE PROSTATE HEALTH INDEX (phi)

Indication for Use

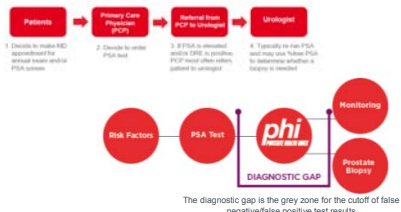
- › Men > 50 years of age
- › Negative DRE
- › PSA range of 4-10 ng/mL



© 2018 Beckman Coulter. All rights reserved.



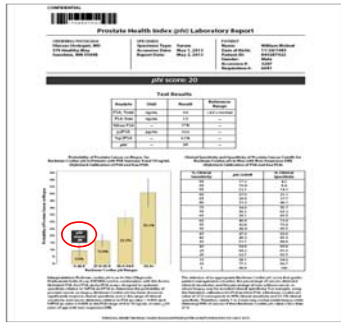
GUIDING THE PATIENT JOURNEY



© 2018 Beckman Coulter. All rights reserved.



REPORTING *phi*



© 2018 Beckman Coulter. All rights reserved.



P2PSA & *phi* PUBLICATIONS

- › Over 90 peer-reviewed journal publications to date on p2PSA and the Prostate Health Index (*phi*)
- › Numerous posters and abstracts presented on p2PSA and *phi* at society conferences (e.g., AUA, EAU, JUA, and AACC)

© 2018 Beckman Coulter. All rights reserved.



***phi* RESEARCH AND CLINICAL STUDIES**

The Prostate Health Index is indicated for use for men aged 50 years with non-suspicious DRE findings in the PSA range of 4-10 ng/mL*

* US Code
 * p2PSA Instructions for Use (REF 833194) Beckman Coulter, Inc.

© 2018 Beckman Coulter. All rights reserved.

phi RESEARCH & CLINICAL STUDIES

Checkmate 513
Nov 2017 (2017)

Cancer Diagnostics

Multicenter Evaluation of [-2]Prostate-Specific Antigen and the Prostate Health Index for Detecting Prostate Cancer
Garten Tzipori^{1,2*}, Michael Vlodavsky³, Alan Hershwitz⁴, Fleming Commons⁵, Wen Wang¹ and Ben Bergeron¹

- › Multicenter, nonrandomized case control trial (n=1362 from four different study sites)
- › The phi score was significantly higher in all PCa subcohorts (positive initial or repeat biopsy result or negative DRE) compared with patients without PCa
- › The phi score had the largest area under the ROC curve (AUC = 0.74)

US Claim: The Prostate Health Index is indicated for use for men aged ≥50 years with non-suspicious DRE findings in the PSA range of 4-10 ng/mL.
-p2PSA Instruction for Use (REF 803704) Beckman Coulter, Inc.

© 2018 Beckman Coulter. All rights reserved. **More Insights Revealed.** **BECKMAN COULTER**

phi RESEARCH & CLINICAL STUDIES

DE GRUYTER
On Open Access (2018), vol.

Taylor Eltahir¹, Laura Fil, Joseph Maria Agui, Rafael Medina and Juan Alvarez
Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer

- › The best performance was observed for %p2PSA and phi, obtaining an AUC of 0.723 and 0.732, respectively.
- › Using the cut-off of 32 for phi, a reduction of 19% biopsies could be obtained
- › Among patients with PCa, phi and %p2PSA values are significantly higher (p < 0.0001) in patients with a biopsy Gleason score ≥ 7.

US Claim: The Prostate Health Index is indicated for use for men aged ≥50 years with non-suspicious DRE findings in the PSA range of 4-10 ng/mL.
-p2PSA Instruction for Use (REF 803704) Beckman Coulter, Inc.

© 2018 Beckman Coulter. All rights reserved. **More Insights Revealed.** **BECKMAN COULTER**

phi RESEARCH & CLINICAL STUDIES

Prostate Cancer and Prostate Disease (2018), 17, 70-74
© 2018 Wolters Kluwer Publishers | Lippincott Williams & Wilkins | DOI: 10.1097/PSA.0000000000000514
www.mdedge.com

ORIGINAL ARTICLE
[-2]proPSA is an early marker for prostate cancer aggressiveness
Hesteggen¹, H Klöcker², E Seiler³, V Skoditz⁴, M Lubner⁵, R Pichler⁶, G Schäfer⁷, W Hönninger⁸ and J Bebbke⁹

- › [-2]proPSA levels were significantly higher in the cancer group (n=208) than in the benign group (n=173)
- › Already 4 years before diagnosis [-2]proPSA differed significantly between PCa and benign prostate in all measured time points
- › When stratified [-2]proPSA levels according to Gleason Score of RP specimens, [-2]proPSA was highest in patients with GS8 and lowest in those with GS6

US Claim: The Prostate Health Index is indicated for use for men aged ≥50 years with non-suspicious DRE findings in the PSA range of 4-10 ng/mL.
-p2PSA Instruction for Use (REF 803704) Beckman Coulter, Inc.

© 2018 Beckman Coulter. All rights reserved. **More Insights Revealed.** **BECKMAN COULTER**

phi RESEARCH & CLINICAL STUDIES



The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer

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

- > 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
> 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

© 2018 Beckman Coulter. All rights reserved.



Horizontal lines for notes

phi RESEARCH & CLINICAL STUDIES



Clinical performance of serum (2)Zn(2+)PSA derivatives, t(2)pPSA and PHI, in the detection and management of prostate cancer

A systematic review of the available scientific evidences was performed to evaluate the potentials of %p2PSA and phi in clinical application.

- > 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

© 2018 Beckman Coulter. All rights reserved.



Horizontal lines for notes

phi RESEARCH & CLINICAL STUDIES

The Melbourne Consensus Statement on the early detection of prostate cancer

Declan G. Murphy, Thomas Ahlerting, William J. Colston, Helen Cowie, Jane Crowe, Noel Clarke, Matthew Cooperberg, David Gillott, Martin Gleaves, Stacy Kadl, Monique Riedinger, Oliver Sartor, Tom Pickles, Aude Woodhull, Patrick C. Walsh and Anthony J. Costello

From Melbourne Consensus Centre, Royal Melbourne Hospital, University of Melbourne, Epworth Prostate Centre, Australian Prostate Cancer Research Centre, Epworth Healthcare, Richmond, Melbourne, VIC, Australia; School of Medicine, University of California, Irvine, Northridge, University of Maryland School of Medicine, Chicago, IL, USA; Dana-Farber Cancer Institute, Boston, MA, USA; University of Queensland, St. Leonards, NSW, Australia; Centre for Prostate Health, University of Queensland, St. Leonards, NSW, Australia; Centre for Prostate Health, University of Queensland, St. Leonards, NSW, Australia; The James Cookson Early Oncology Institute, Johns Hopkins University, Baltimore, MD, USA; The Charles M. Storz Prostate Cancer Research Center, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA; The Vancouver Prostate Centre, BC Cancer Agency, University of British Columbia, Vancouver, Canada; and "National University Medical Center, Baltimore, The Netherlands

Prostate cancer is the most common cancer among men in Australia and the United States. In 2017, 32,000 men were diagnosed with prostate cancer in Australia and 50,000 in the United States. Prostate cancer is a leading cause of cancer death in men in Australia and the United States. The Melbourne Consensus Statement on the early detection of prostate cancer provides a framework for the early detection of prostate cancer. The statement is based on the Melbourne Consensus Statement on the early detection of prostate cancer. The statement is based on the Melbourne Consensus Statement on the early detection of prostate cancer. The statement is based on the Melbourne Consensus Statement on the early detection of prostate cancer.

- > PSA testing should not be considered on its own, but as a part of a multivariable approach
> phi can help to better risk stratify men, potentially reducing over-diagnosis and over-treatment of indolent prostate cancer.

© 2018 Beckman Coulter. All rights reserved.



Horizontal lines for notes

NCCN 2014/2016 GUIDELINE UPDATES: *phi*



- › In March 2014, NCCN issued new guidelines for prostate cancer early detection
- › *phi* included as a marker of specificity for PCa
- › A *phi* score of >35 is strongly suspicious for PCa
- › In January 2016, NCCN recommended active surveillance for Gleason Score of 7 (3+4), where *phi* can play an important role

© 2018 Beckman Coulter. All rights reserved.





A RECENT STUDY



- › Study Results:
 - › Physicians elected not to biopsy men presented in the diagnostic grey zone when *phi* testing was included in their overall assessment, resulting in a net 24% reduction in biopsies performed compared to their historical practice.
 - › Physicians reported that *phi* testing significantly impacted their patient management decision in over 73% of cases.

© 2018 Beckman Coulter. All rights reserved.




SUMMARY

- > *phi* makes PSA a better marker
- > Improves the probability of finding prostate cancer on biopsy
- > Improves patient management decisions
- > *phi* may reduce healthcare costs by reducing the number of negative biopsies (est. 31%)
- > A role for *phi* in active surveillance has been strongly suggested and studies continue

©2PSA Instructions for Use (REF B03704) Beckman Coulter, Inc.

© 2018 Beckman Coulter. All rights reserved.



THANK YOU

© 2018 Beckman Coulter. All rights reserved.





**BECKMAN
COUTLER**

© 2018 Beckman Coulter. All rights reserved.
