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Cleveland Diagnostics
the future in cancer diagnostics

IsoPSA™ Prospective Study Interim Analysis

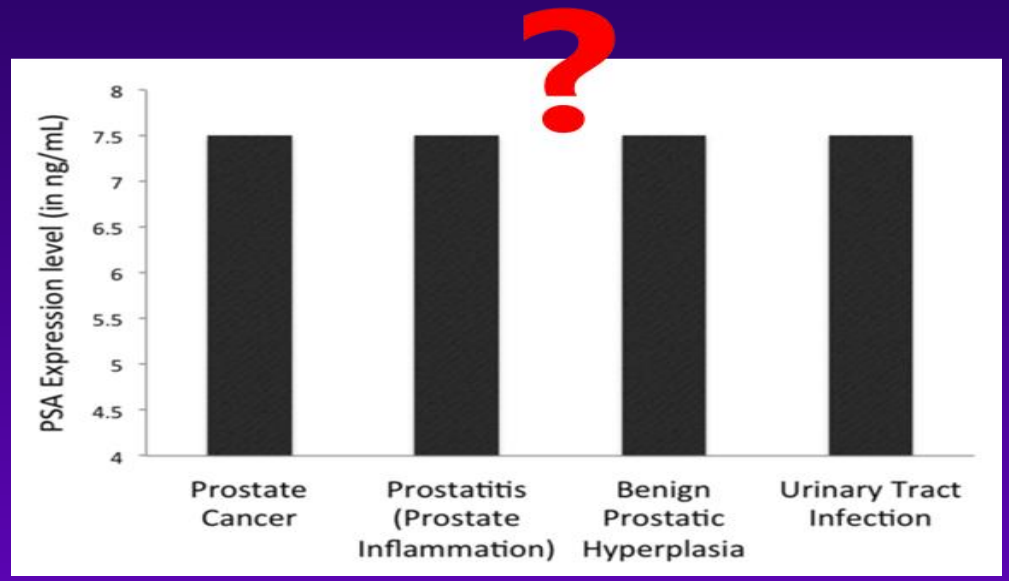
7/13/2016

Cleveland Diagnostics

Key Issues in Screening & Diagnosis

To be clinically useful, a biomarker must be specific to both <u>tissue type</u> AND to <u>cancer</u>

- **PSA & kallikreins are prostate specific but not cancer specific**
- **Diagnostic accuracy, predictive value, and clinical utility of current biomarkers are limited by**
  - **lack of cancer specificity**
  - **relatively poor sensitivity**



PSA has multiple structural isoforms that are cancer specific

Biomarker Structure vs. Concentration

- Biomarkers produced by cancer cells
  - Different 3D structure than the same proteins produced in normal cells
    - Truncations (proPSA)
    - Post-translational modifications (glycosylation)

- There is ample literature on structural changes to PSA in cancer
  - ~ 100s-1000s of PSA isoforms in serum

- Current screening assays measure only the ***concentration*** of a limited number of these isoforms

- IsoPSA measures both ***structure*** and ***concentration***

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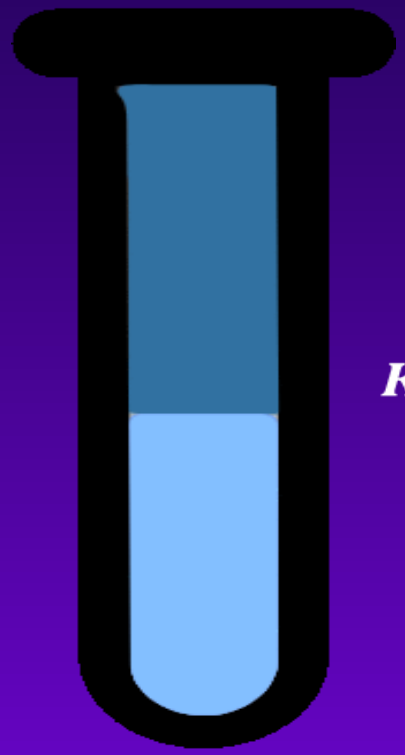
IsoPSA assayed by Solvent Interaction Analysis (SIA)

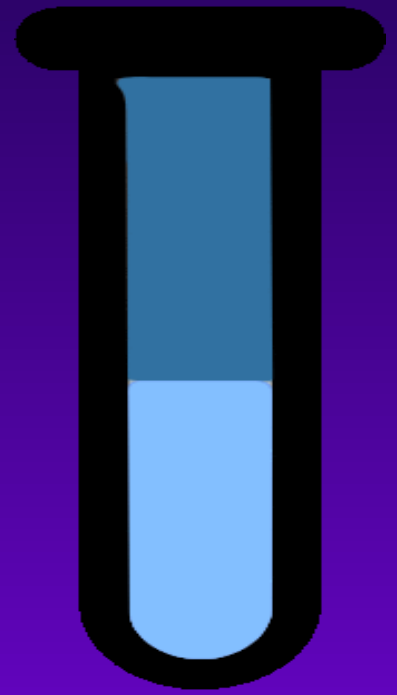
- Novel assay using proprietary aqueous-based solvents to detect overall changes in the structure or isoform mixtures of biomarkers
- Interrogates entire PSA isoform distribution in serum as opposed to pre-selecting individual protein biomarkers
- Reports an overall index to the structure, K
- Add on to tPSA/fPSA assay, performed on same sample before standard ELISA at low cost
- Results independent of tPSA



$$K = \frac{[C_{bottom}]}{[C_{top}]}$$

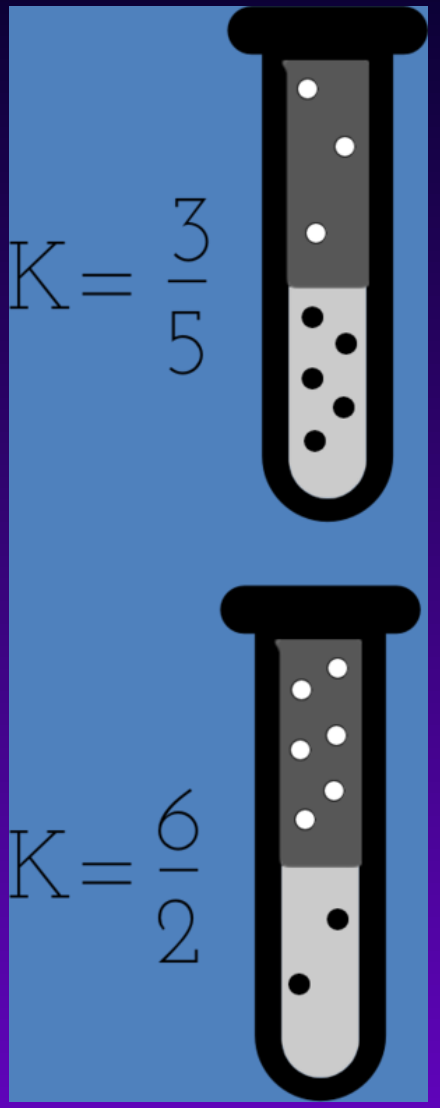
Separation based on structural ***change***

- A sample is first placed in the aqueous two-phase system.
- The system is agitated and then centrifuged to thoroughly mix and then separate the solutes.
- Protein isoforms partition unequally between the top and bottom phases based on their *structure*.



K Value

- K is the output of SIA
- Represents the quantitative ratio of the biomarker concentration in each phase.
- K is independent of the total biomarker concentration.
- The value of K corresponding to cancer and benign disease states is calibrated against known clinical samples diagnosed by biopsy.
- The biomarker concentration in each phase is measured with immunoassay.



IsoPSA™ Multicenter Prospective Study: Interim Snapshot

- Principal Investigator:
  - Eric Klein, MD, Chairman, Glickman Urology and Kidney Institute, Cleveland Clinic
- Participating Institutions:
  - Cleveland Clinic Foundation
  - Louis Stokes VA Medical Center – Cleveland
  - Michigan Urology Institute
  - Chesapeake Urology
  - National Hospital – Abuja, Nigeria

Objective:

- Assess clinical performance of IsoPSA against gold-standard 12 core TRUS prostate biopsy

Study Protocol:

- IRB approved protocol (national & site-specific)
- Serum/plasma obtained from volunteers already selected for prostate biopsy according to current medical criteria
- IsoPSA clinical performance is evaluated using standard statistical techniques
- IsoPSA is tested alone, or in combination with other parameters for various clinical needs

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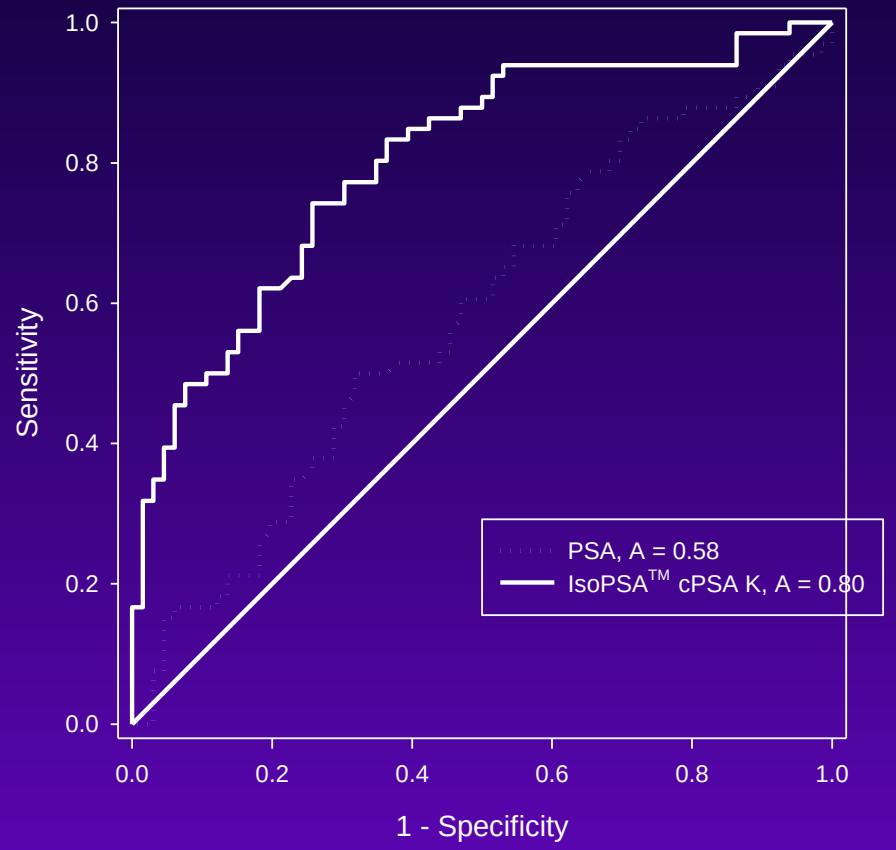
Study Summary

Sample Cohort	132 prospective patient samples collected prior to prostate biopsy. Subjects were selected for biopsy on the basis of an abnormal peripheral blood PSA level (total PSA, age specific PSA, PSA velocity, free PSA fraction, etc.) and/or other clinical presentations including an abnormal prostate digital rectal examination.
Study Protocol	– Plasma and Serum were collected from each patient – tPSA, %fPSA, and IsoPSA™ K were determined in serum and plasma for each patient
Data Analysis	– To evaluate the diagnostic accuracy of IsoPSA™ for all prostate cancer (Gleason Score ≥ 6(3+3)) ROC analysis was applied to tPSA and IsoPSA™ conducted on complex PSA (cPSA) and the outcome of prostate cancer as determined by biopsy. The sensitivity, specificity and predictive value is compared between IsoPSA™ conducted with cPSA and for tPSA. – To evaluate the diagnostic accuracy of IsoPSA™ for more aggressive prostate cancer (Gleason Score ≥ 7(3+4)). ROC analysis was applied to IsoPSA™ and the outcome of the more aggressive prostate cancer for all patients as determined by biopsy. The sensitivity, specificity and predictive value is compared for IsoPSA™conducted with cPSA and tPSA.

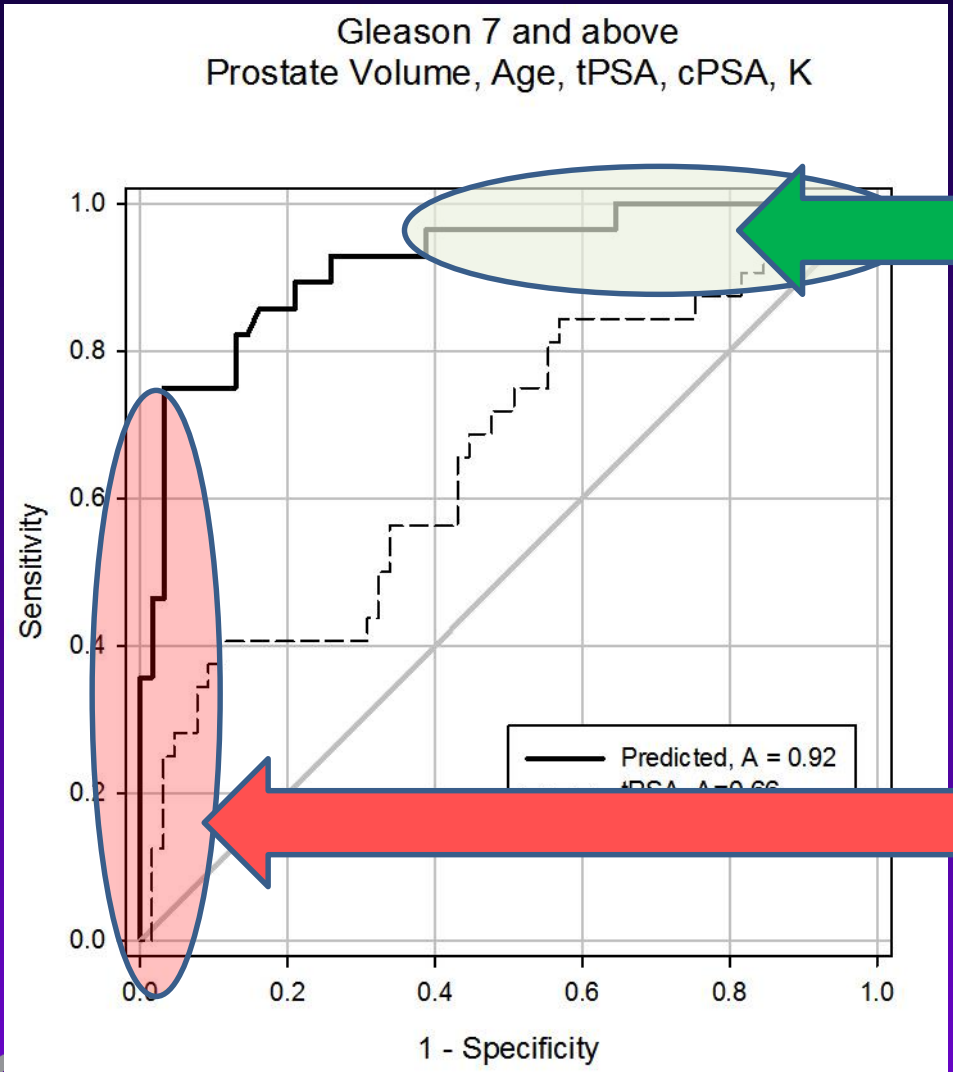
IsoPSA 6 (Single Parameter, K): Any Cancer



	PSA	IsoPSA 6
Cut-off	4 ng/ml	8
Sensitivity	91%	94%
Specificity	12%	47%
NPV	57%	88%
PPV	51%	64%
AUC	0.58	0.80

Single parameter, K, representing an index to the overall structure of PSA, has excellent discrimination power

Multi-Variate Model – Gleason ≥ 7



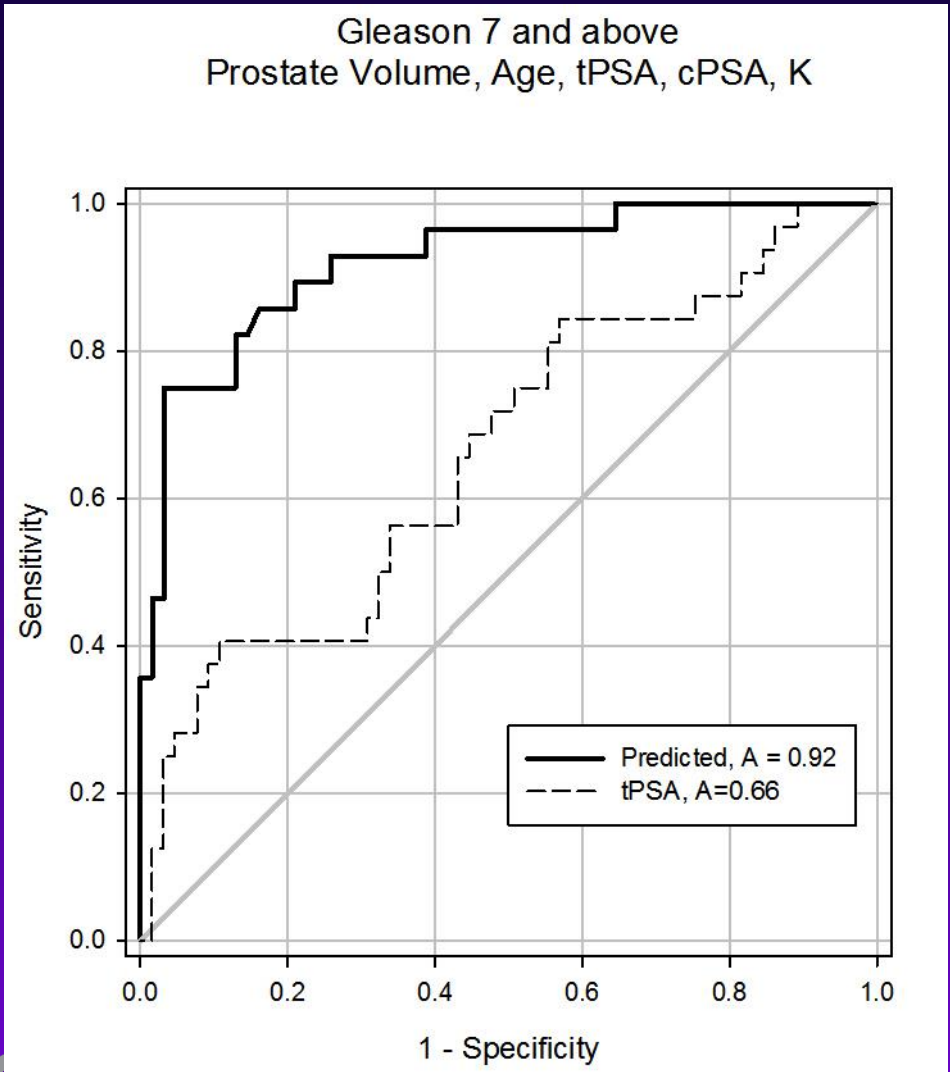
Very high NPV:

Negligible chance for aggressive cancer

Very high PPV:

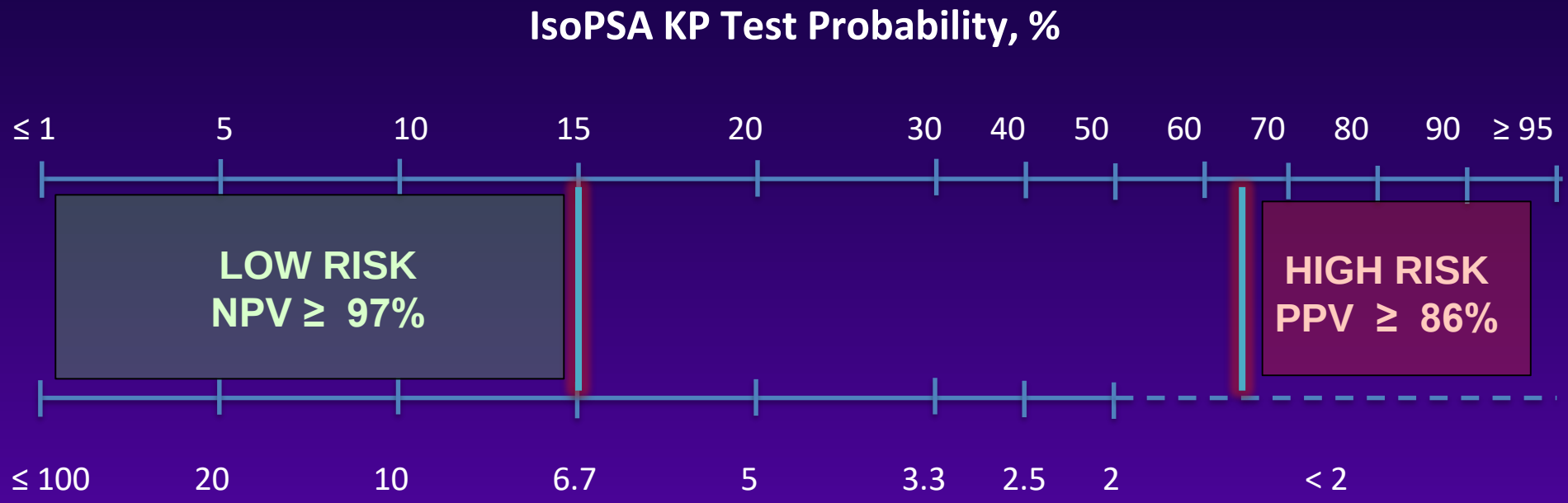
High chance for aggressive cancer

Multi-Variate Model – Gleason ≥ 7



	PSA	IsoPSA 7	IsoPSA 7
Cohort		Low Risk	High Risk
Prevalence	34%	34%	34%
Cut-off	4 ng/ml	< 15%	>64%
Sensitivity	91%	97%	47%
Specificity	13%	47%	96%
NPV	68%	97%	78%
PPV	35%	49%	86%
AUC	0.61	0.85	0.85

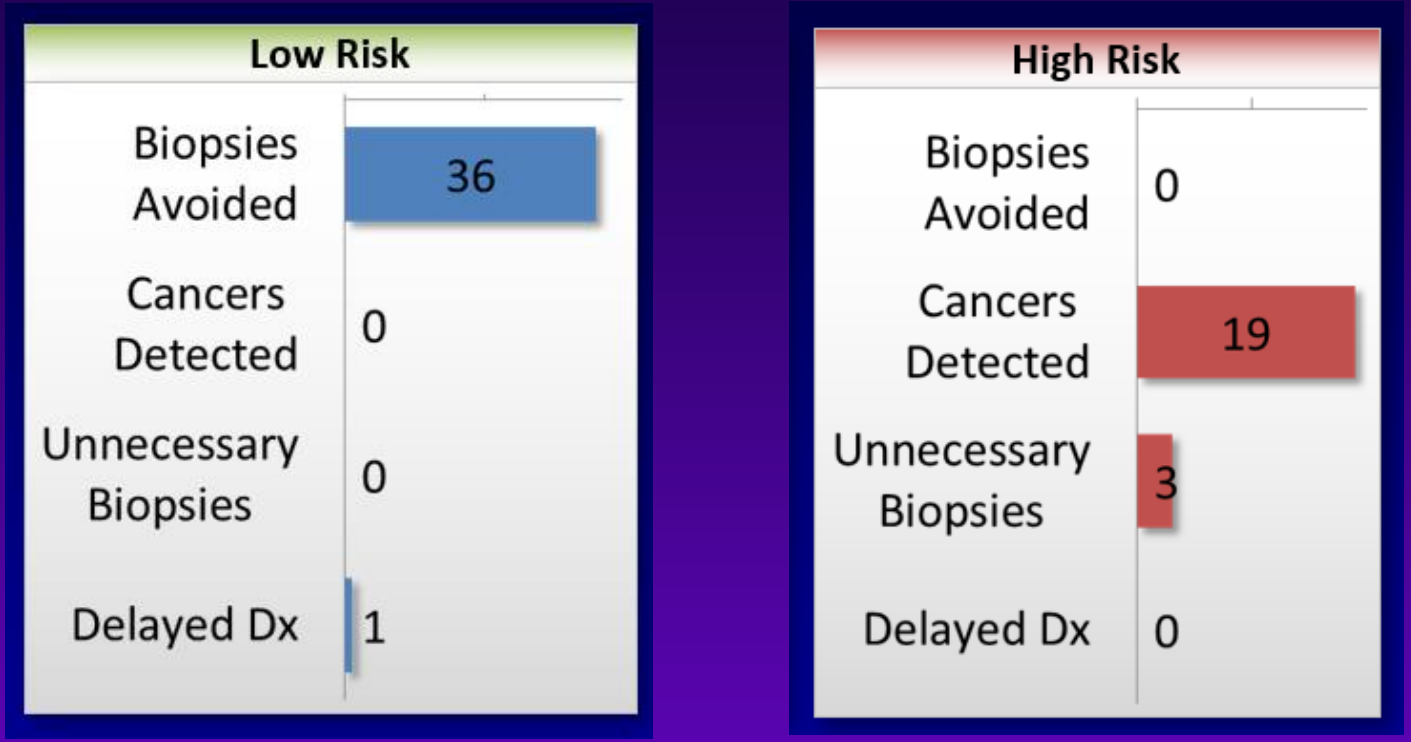
Probabilistic Clinical Interpretation



Reduction in unnecessary biopsies: **52%**
Missed high risk patients: **None**
Correct identification of low risk patients: **97%**

Clinical Significance

Risk of Gleason 7 or greater



- **Reduction in unnecessary biopsies: 52%**
- **Missed high risk patients: None**
- **Correct identification of low risk patients: 97%**

On-Going Study: Key Aims

- Patient selection for primary biopsy
- Potential utility
  - Reflex test for repeat biopsy
  - Head to head comparison vs. other available markers
  - Prediction of high grade/biologically aggressive disease
  - Prediction of adverse pathologic stage on RP
  - Serial individual monitoring (% change in IsoPSA)
  - Performance & discrimination in subpopulations
    - AA, younger patients, germline risk

Press Releases Following AUA

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New PSA test examines protein structures to detect prostate cancers

Interim analysis shows novel test can detect malignancies and differentiate between high-grade, low-grade prostate cancer

Date: May 11, 2016

Source: Cleveland Clinic

Summary: A promising new test is detecting prostate cancer more precisely than current tests, by identifying molecular changes in the prostate specific antigen (PSA) protein, according to new research.

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New PSA Test Examines Protein Structures To Detect Prostate Cancers

Interim analysis shows novel test can detect malignancies and differentiate between high-grade, low-grade prostate cancer

MAY 10, 2016 / NEWS RELEASES

San Diego: A promising new test is detecting prostate cancer more precisely than current tests, by identifying molecular changes in the prostate specific antigen (PSA) protein, according to Cleveland Clinic research presented today at the American Urological Association annual meeting.

The study – part of an ongoing multicenter prospective clinical trial – found that the IsoPSA test can also differentiate between high-risk and low-risk disease, as well as benign conditions.

Although widely used, the current PSA test relies on detection strategies that have poor specificity for cancer – just 25 percent of men who have a prostate biopsy due to an elevated PSA level actually have prostate cancer, according to the National Cancer Institute – and an inability to determine the aggressiveness of the disease.

The IsoPSA test, however, identifies prostate cancer in a new way. Developed by Cleveland Clinic, in collaboration with Cleveland Diagnostics, Inc., IsoPSA identifies the molecular structural changes in protein biomarkers. It is able to detect cancer by identifying these structural changes, as opposed to current tests that simply measure the protein's concentration in a patient's blood.

"While the PSA test has undoubtedly been one of the most successful biomarkers in history, its limitations are well known. Even currently available prostate cancer diagnostic tests rely on biomarkers that can be lated to cancer," said Eric Klein, M.D., chair of Cleveland Clinic's le. "These study results show that using structural changes in PSA ive and can help prevent unneeded biopsies in low-risk patients."

re institutions and 132 patients, to date. It examined the ability of d without biopsy-confirmed evidence of cancer. It also evaluated the nts with high-grade (Gleason ≥ 7) cancer from those with low-grade lings after standard ultrasound-guided biopsy of the prostate.

ed composite index for the standard PSA resulted in improvement in erum PSA testing, IsoPSA performed better in both sensitivity and

that has shown success in detecting prostate cancer but also has the portant questions such as clinical surveillance of patients after taff member, Cleveland Clinic Glickman Urological & Kidney vsky has a leadership position (Chief Medical Officer) and investment . "In general, the clinical utility of prostate cancer early detection and fact that biomarker concentrations may be affected by physiological

MED НОВОСТИ

Как пи
кишечн

ПСА-тест может быть усовершенствован

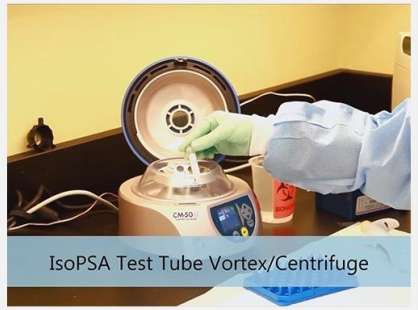

Фото: Arnon Chait/Youtube.com

12 мая 2016 года, 13:20

КОММЕНТИРОВАТЬ

ЧИТАТЬ ЕЩЕ: РАК ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

Многие онкологические ассоциации отказались от введения ПСА-теста в обяз
Тест, в котором определяется концентрация простатического специфического
выявлении рака предстательной железы. Повышение концентрации ПСА мо
причинами и не всегда виной тому рак. На уровень биомаркера может влиять
Лишь у 25% мужчин, которым пришлось пройти процедуру биопсии предстат

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New IsoPSA test identifies molecular structural changes in protein biomarkers to detect prostate cancer

Published on May 12, 2016 at 4:21 PM · No Comments

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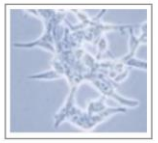
A promising new te
identifying molecul
to Cleveland Clinic
annual meeting.

CANCER de la PROSTATE: IsoPSA, le nouveau test PSA qui identifie les tumeurs bénignes

Actualité publiée hier

Meeting American Geriatrics Society (AGS)



On connaît les limites du test PSA, et même ses dangers, avec les risques de sur-diagnostic, sur-biopsie et sur-traitement. Bien que devant aujourd'hui être l'objet d'une décision éclairée médecin-patient, toujours utilisé comme un outil de dépistage de masse (y compris en France), le dosage du PSA entraîne

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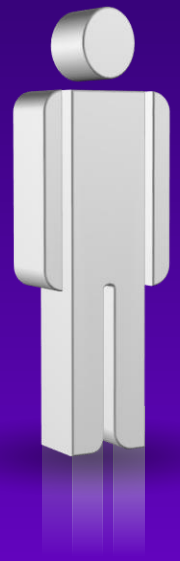
Nuevo test detecta el cáncer de próstata a través de la estructura de las proteínas

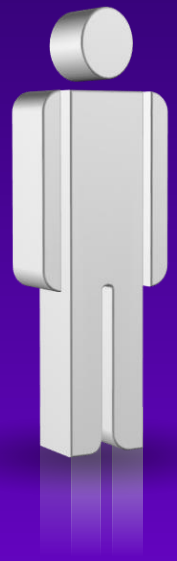
TI/Innovación mayo 12, 2016

Urology Indications: Case Study



Patient 201

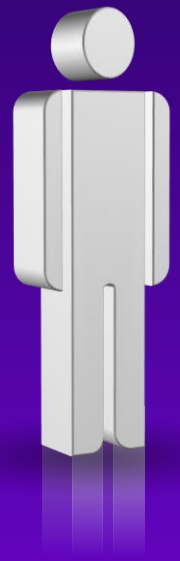
Age…….	46
Race……..	African American
tPSA……..	3.0 ng/mL
%fPSA…..	14.1%
Prostate Volume…	34 g



Patient 68

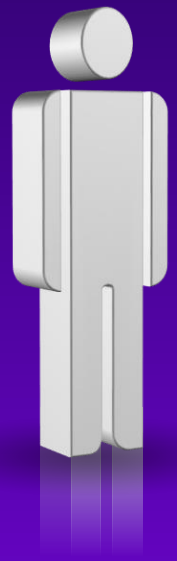
Age…….	50
Race……..	White
tPSA……..	3.8 ng/mL
%fPSA…..	11.2%
Prostate Volume…	40 g

Urology Indications: Case Study
IsoPSA™ 7 Results



Patient 201

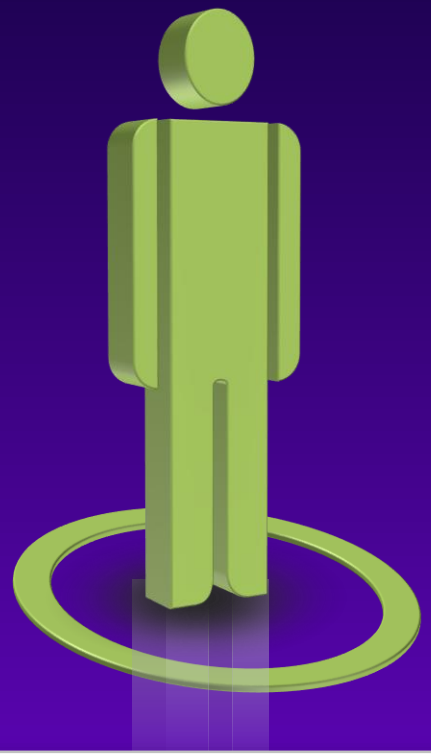
Age.....	46
Race.....	African American
tPSA.....	3.0 ng/mL
%fPSA.....	14.1%
Prostate Volume.....	34 g
IsoPSA™ 7....	Low Risk



Patient 68

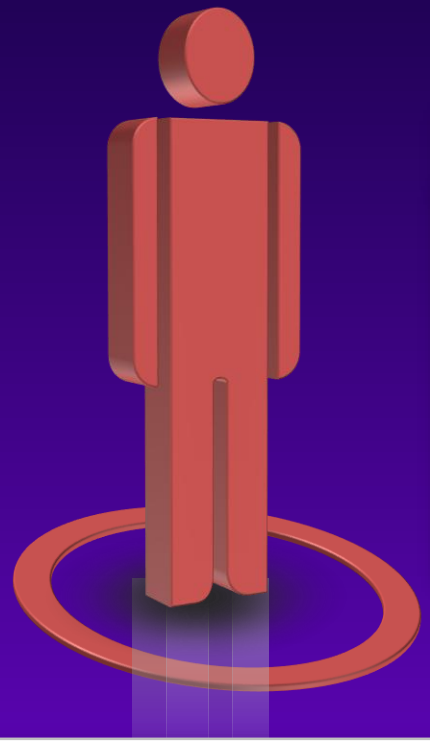
Age.....	50
Race.....	White
tPSA.....	3.8 ng/mL
%fPSA.....	11.2%
Prostate Volume.....	40 g
IsoPSA™ 7....	High Risk

Urology Indications: Case Study
Biopsy Results



Patient 201 - Pathology	
Primary Dx....	HGPIN
Gleason Score.....	N/A
No. of Malignant Cores.....	N/A
% Malignant.....	N/A

IsoPSA™ 7: Low Risk

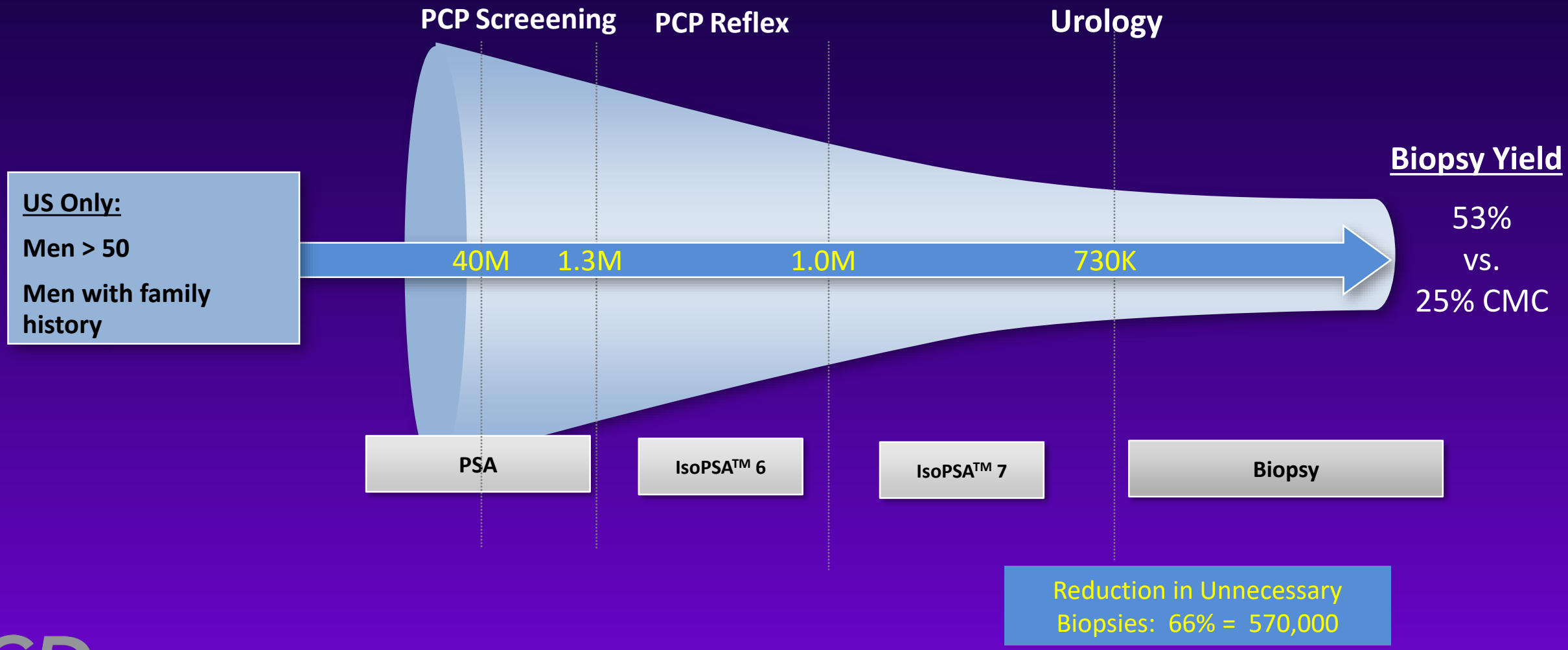


Patient 68 - Pathology	
Primary Dx.....	CaP
Gleason Score.....	7(3+4)
No. of Malignant Cores.....	4
% Malignant.....	60%

IsoPSA™ 7: High Risk

A Combined IsoPSA Screening/Diagnostics Workup

Minimal Performance Scenario



Planned Meetings/Publications

- AUA – Late Breaking Session – May 10, 2016
- AUA – North Central Meeting – September, 2016
- Friends of Israel – July 2016
- Society of Urological Oncology – December 2016
- ASCO-GU
- European Journal of Urology – Fall 2016

Cleveland Diagnostics

Arnon Chait, CEO
440-454-1454

"Nearly every cancer [and neurodegenerative disease] that is caught early is curable."
- Bob Kronemyer