Development of an In Vitro Diagnostic Multivariate Index Assay (IVDMIA) for Aggressive Prostate Cancer

EDRN Biomarker Reference Laboratory (BRL) at Johns Hopkins

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JHU BRL Aims

The goals of the JHU BRL:

- Collaborative studies: Help accelerate the translation of biomarkers into clinical diagnostics by providing resources and support for the analytical and clinical validation of biomarker.
- Product Development: Develop an IVDMIA *(In vitro diagnostic multivariate index assay)* that combines a panel of serum biomarkers into a single-valued numerical index score. It is intended to evaluate the risk of aggressive prostate cancer in men prior to prostate biopsy.

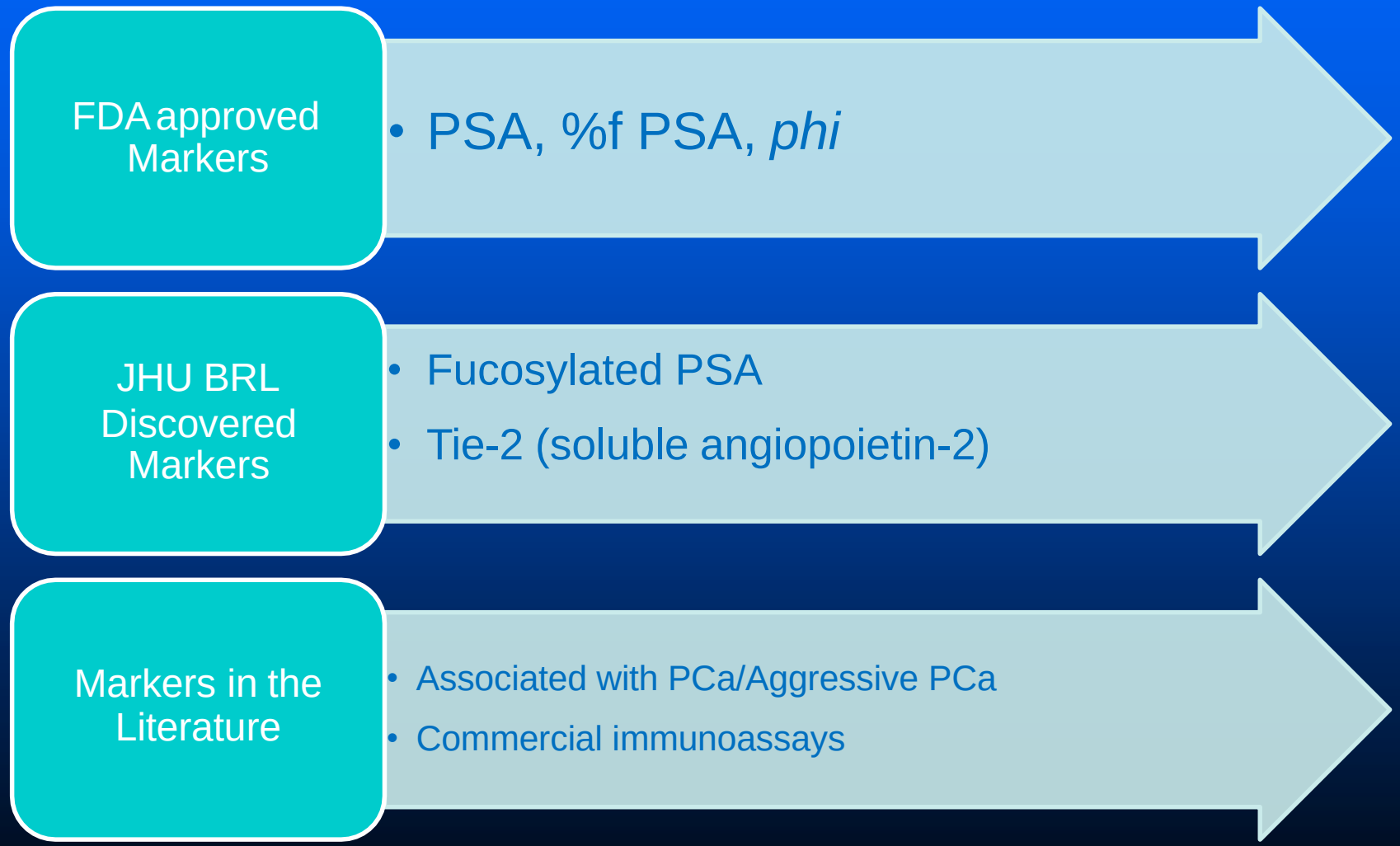
JHU BRL Milestones
Prostate Cancer

Candidate Biomarkers – Prostate					
Candidate Biomarker	**Discovery**			**Pre-validation**	**Validation**
	Discovery	Predictive Analysis	Assay Refinement	Blinded Limited Cross-Sectional	Large Cross-Sectional
BRL-IVDMIA for aggressive prostate cancer					
BRL-MiCheck, Minomic Ltd. Collaboration *CLIA/LDT*					
Collaborative projects- see reports from EDRN lab PIs					
Sanda CVC – Biomarker Panel – *phi* and PCA3					
Sanda CVC – *phi* in PASS study					
UTHSC Liss CVC – *phi* and imaging					
Collaborative group study – Imaging and Biomarkers (PI Wei)					

JHU BRL Milestones
Ovarian, Pancreas, and Liver Cancers

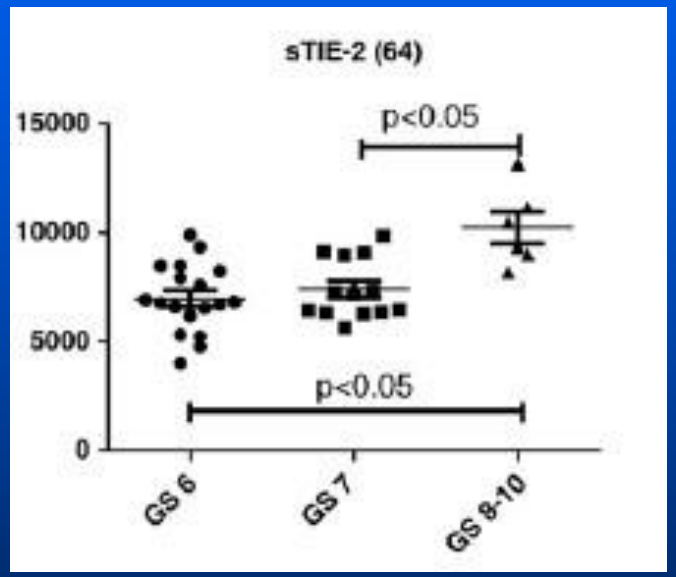
	Discovery			Pre-validation	Validation
	Discovery	Predictive Analysis	Assay Refinement	Blinded Limited Cross-Sectional	Large Cross-Sectional
Candidate Biomarkers - Ovarian					
Collaborative projects- see reports from EDRN lab PIs					
Collaborative group study – Skates, Early detection biomarker panel (PI Skates)					
Collaborative group study – Uterine lavage biomarker panel study (PI Skates)					
Candidate Biomarkers - Pancreas					
BRL-Multiplex Immunoassay panel					
Candidate Biomarkers - Liver					
BRL - Biomarkers panel, Abbott Labs collaboration					

JHU BRL Product Development Biomarker Identification (1)



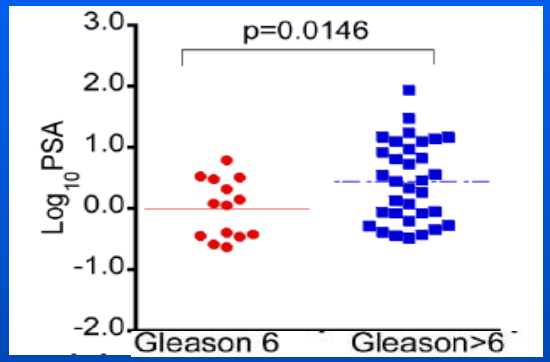
JHU BRL Product Development Biomarker Identification (2)

TIE-2 (soluble angiopoietin-2)

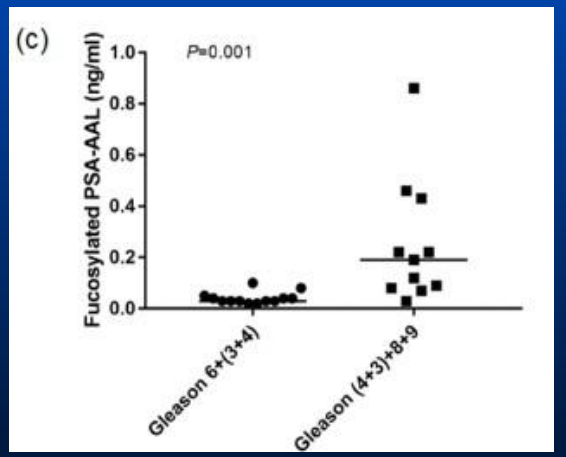


Danni Li, Hanching Chiu, Vinita Gupta, Daniel W. Chan. Clinica Chimica Acta, (2012)413:1506–1511

Fucosylated PSA

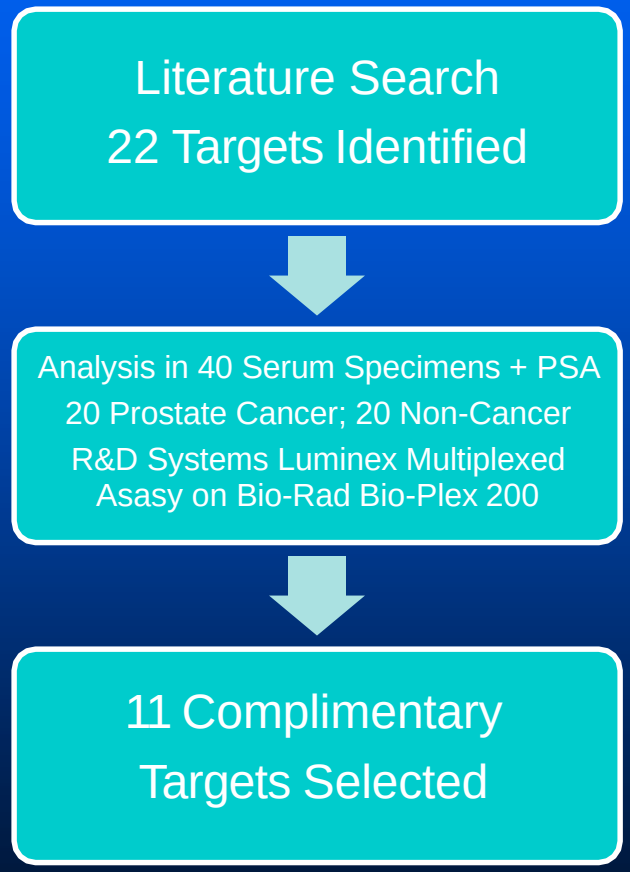


Qing Kay Li, Li Chen, MH Ao, Joyce Chiu, Zhen Zhang, Hui Zhang, Daniel W Chan. Theranostics (2015) 5:267-276.

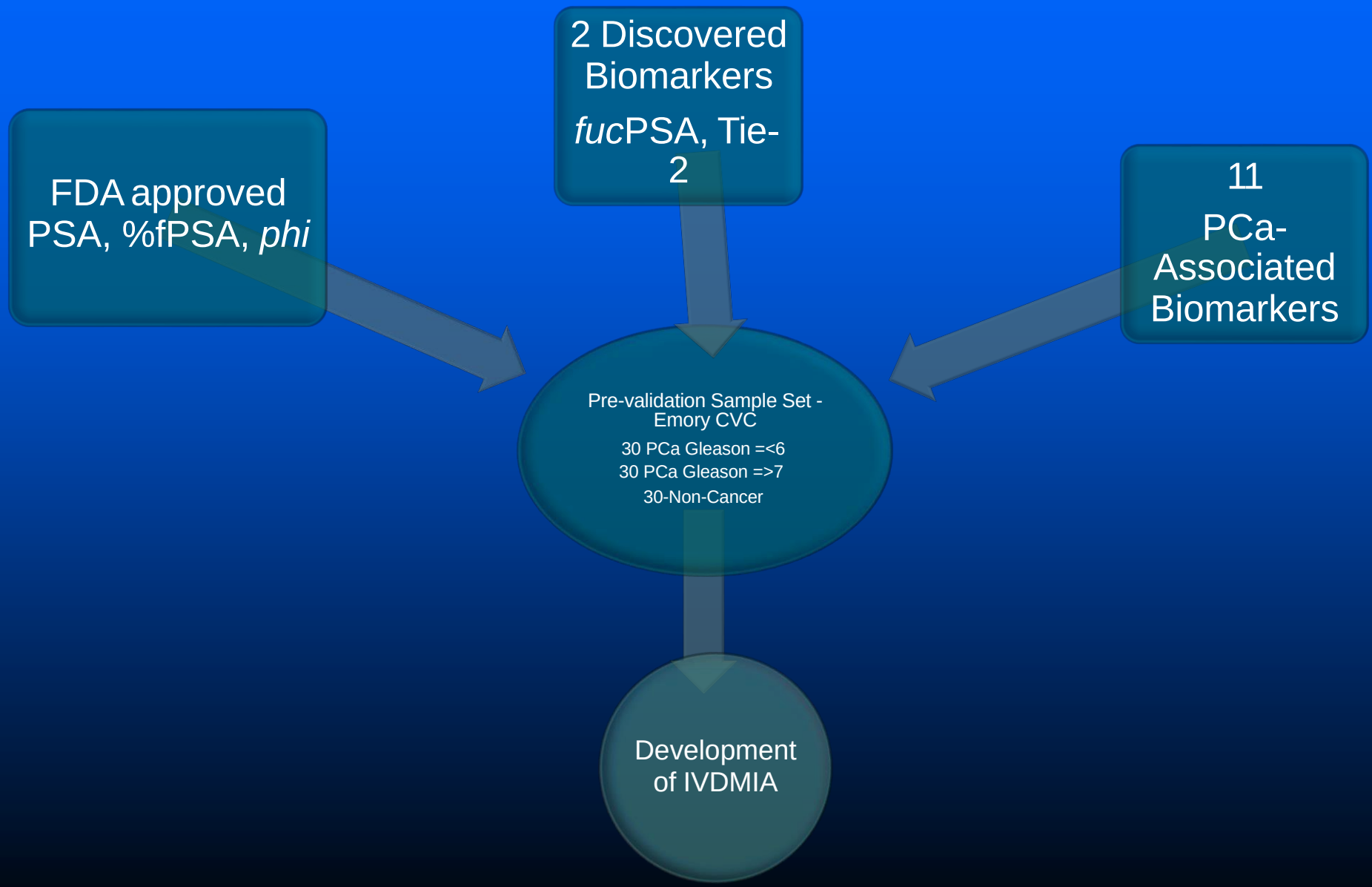


Wang C, Höti N, Lih TM, Sokoll LJ, Zhang R, Zhang Z, Zhang H, Chan DW. Clinical Proteomics. (2019) Apr 6;16:13.

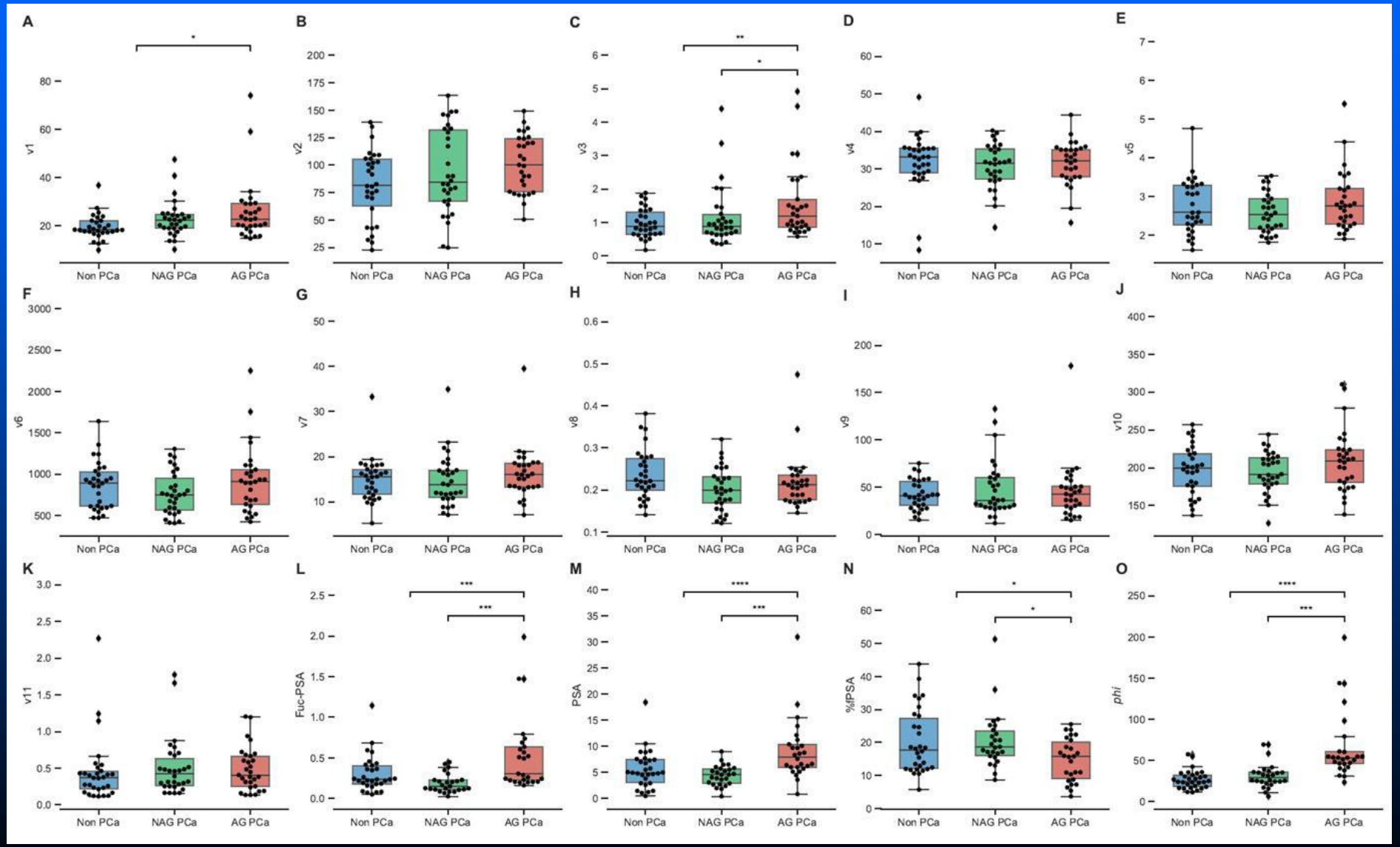
JHU BRL Product Development
Biomarker Identification (3)



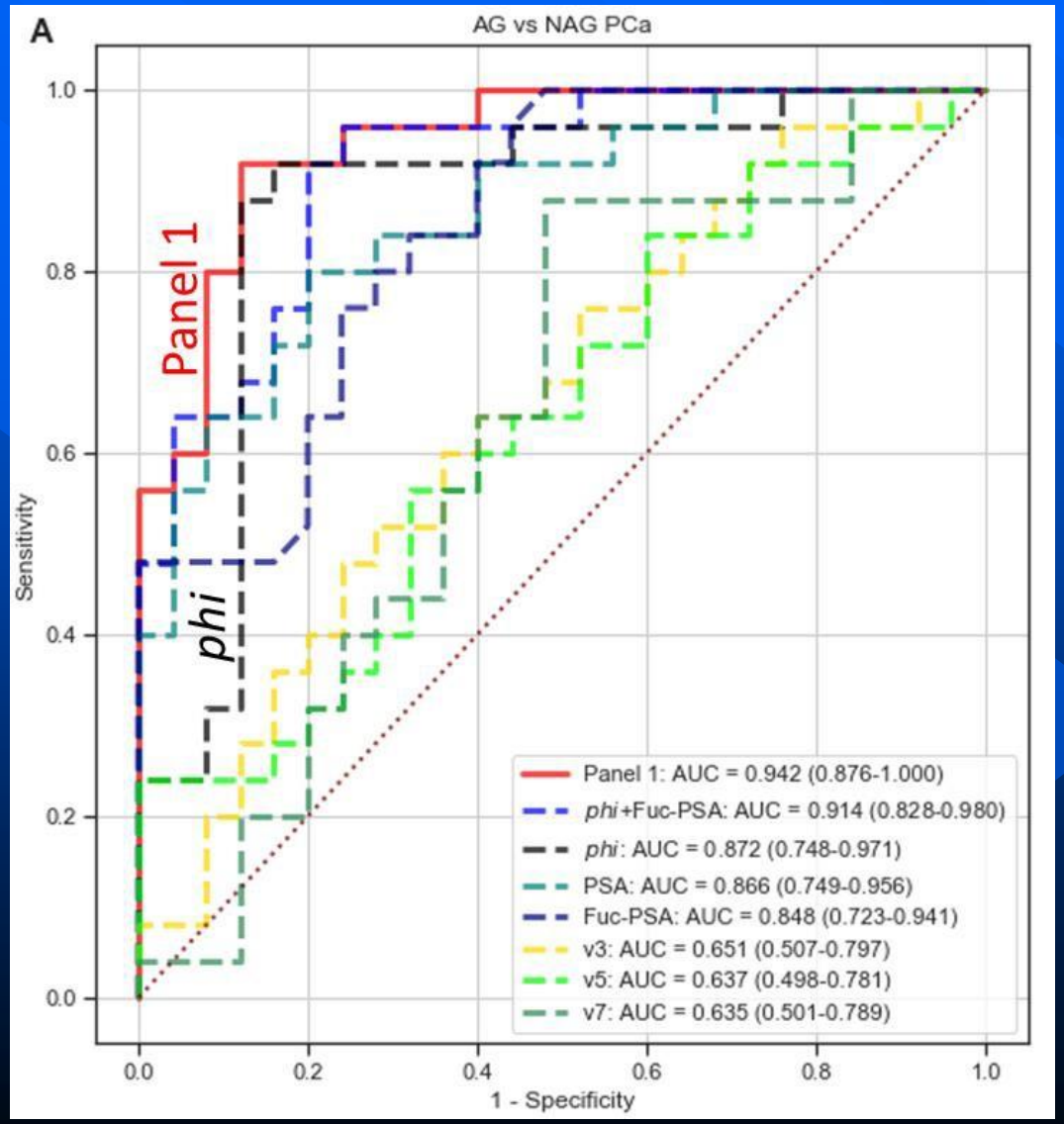
JHU BRL Product Development – Pre-validation



JHU BRL Product Development
Biomarker Distribution

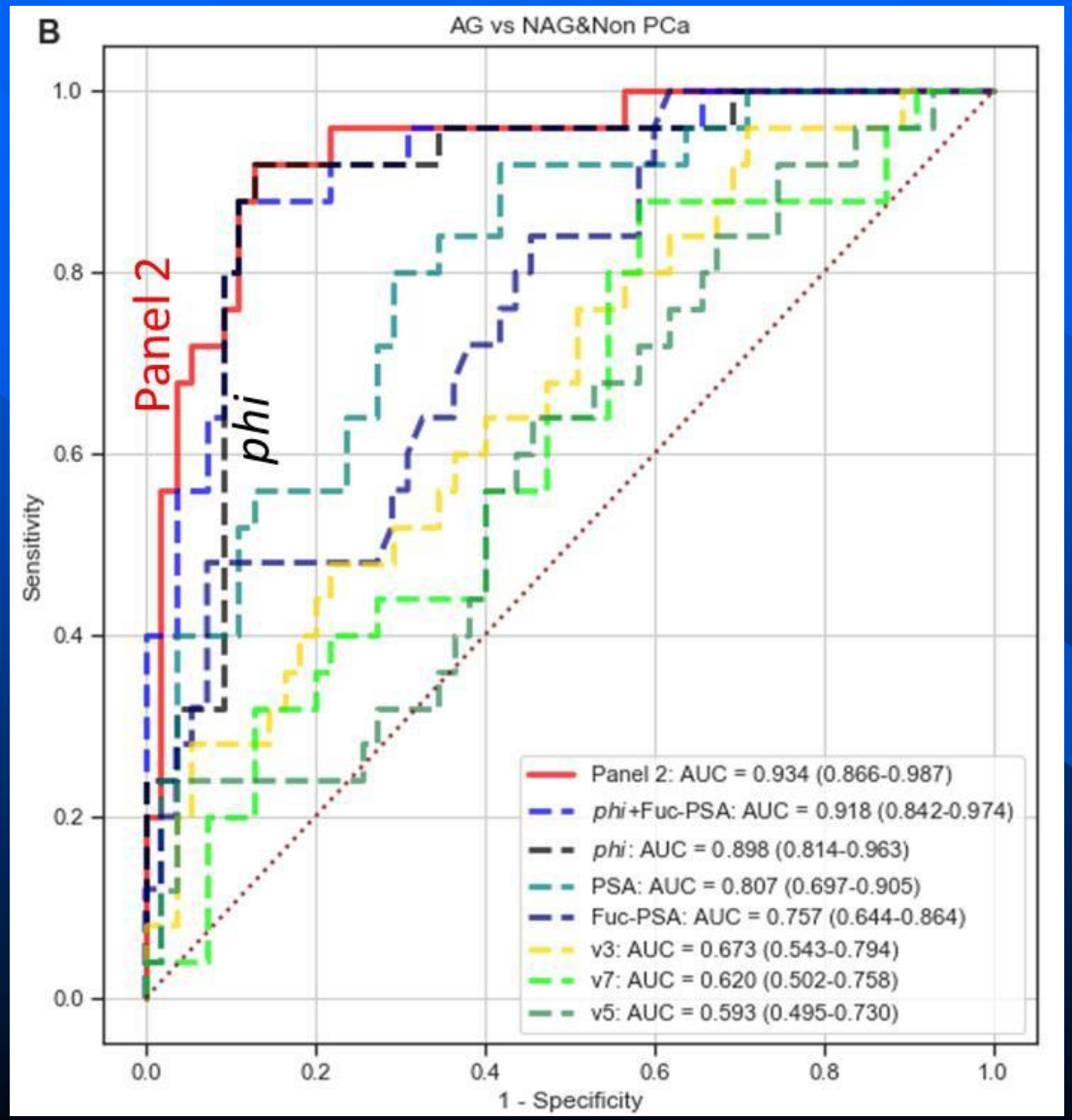


Panel Selection (using backward stepwise multivariate logistic regression): complement *phi* to detect AG from NAG Pca (from bootstrap estimation)



Panel Selection (using backward stepwise multivariate logistic regression): complement phi to detect AG from NAG PCa + non PCa

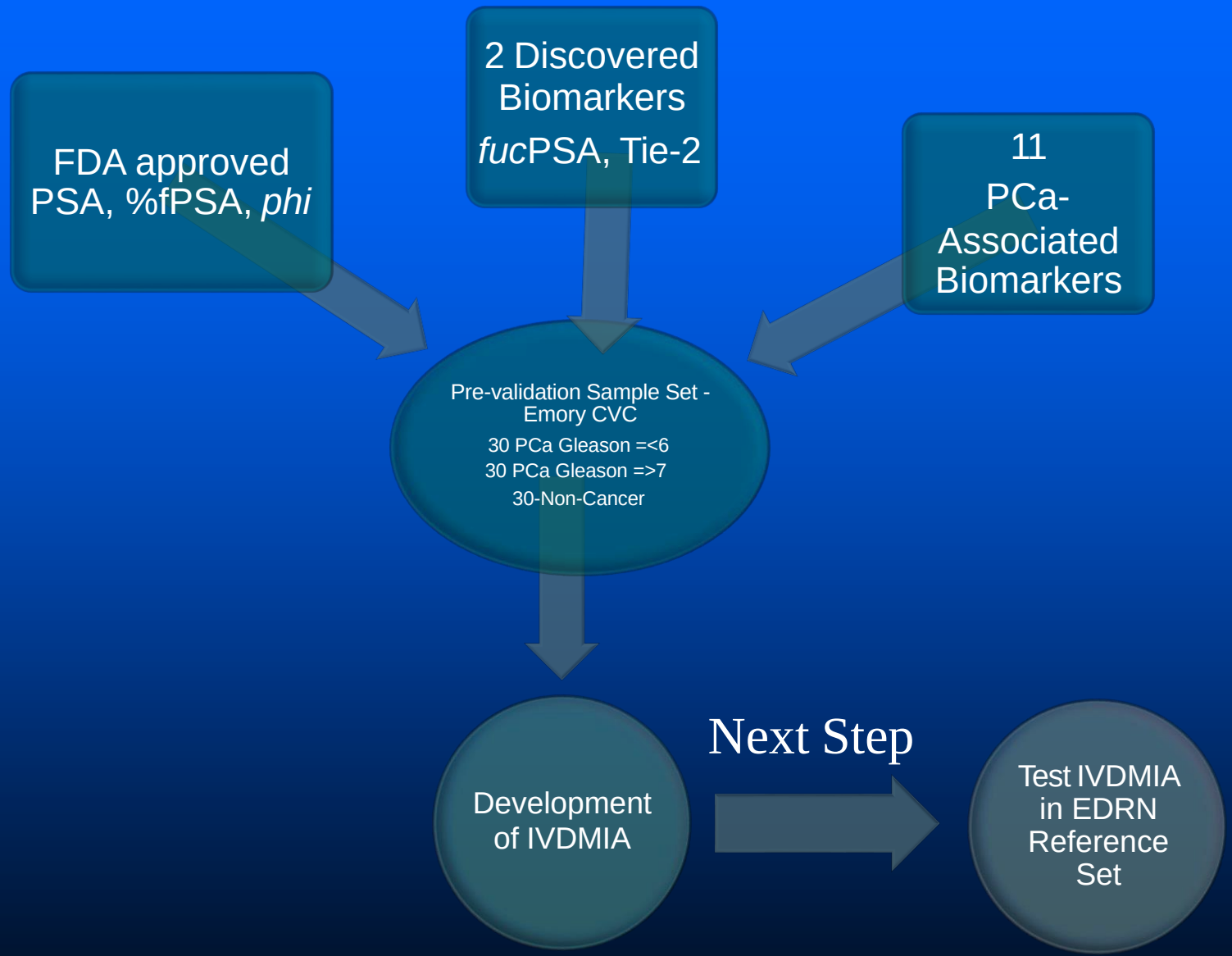
(from bootstrap estimation)



Improvement in specificity at 95% sensitivity

	AUC (95% CI)	SN (%)	SP (%)	Neg	Pos	False-Neg	False-Pos
AG vs NAG							
Panel 1	0.942 (0.876-1.000)	95.0	76.0	19	24	1	6
phi + Fuc-PSA	0.914 (0.828-0.980)	95.0	76.0	19	24	1	6
phi	0.872 (0.748-0.971)	95.0	56.0	14	24	1	11
PSA	0.866 (0.749-0.956)	95.0	44.0	11	24	1	14
AG vs NAG & Non							
Panel 2	0.934 (0.866-0.987)	95.0	78.2	43	24	1	12
phi + Fuc-PSA	0.918 (0.842-0.974)	95.0	69.1	38	24	1	17
phi	0.898 (0.814-0.963)	95.0	65.5	36	24	1	19
PSA	0.807 (0.697-0.905)	95.0	36.4	20	24	1	35

Summary - JHU BRL Product Development



Acknowledgments

JHU BRL Team

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Development and evaluation of the MiCheck test for aggressive prostate cancer

- MiCheck is an IVDMIA for aggressive prostate cancer using a logistic regression model with the following variables: PSA, patient age, DRE, Leptin, IL-7, VEGF, Glypican-1.
- *Shore ND, Pieczonka CM, Henderson RJ, Bailen JL, Saltzstein DR, Concepcion RS, Beebe-Dimmer JL, Ruterbusch JJ, Levin RA, Wissmueller S, Le TH, Gillatt D, Chan DW, Campbell DH, Walsh BJ. Urol Oncol. 2020 Apr 16:S1078-1439(20)30097-1*.
- Developed by Minomic Ltd.
- Agreement with Cirrus Dx, a CLIA lab, MiCheck performed as an LDT (lab developed test).

The MiCheck® Prospective Trial

- Principal Investigator: Dr Neal Shore
- Prospective, non-randomized case-control study at 12 US research centers, 320 subjects
- All subjects proceeding to Prostate Biopsy on the basis of an elevated, age-adjusted PSA score
- Total 320 patients falling in to three groups as follows:

  Group A: 141 patients (44%), no cancer

  Group B: 62 patients (19%), GS = 3+3, CaP

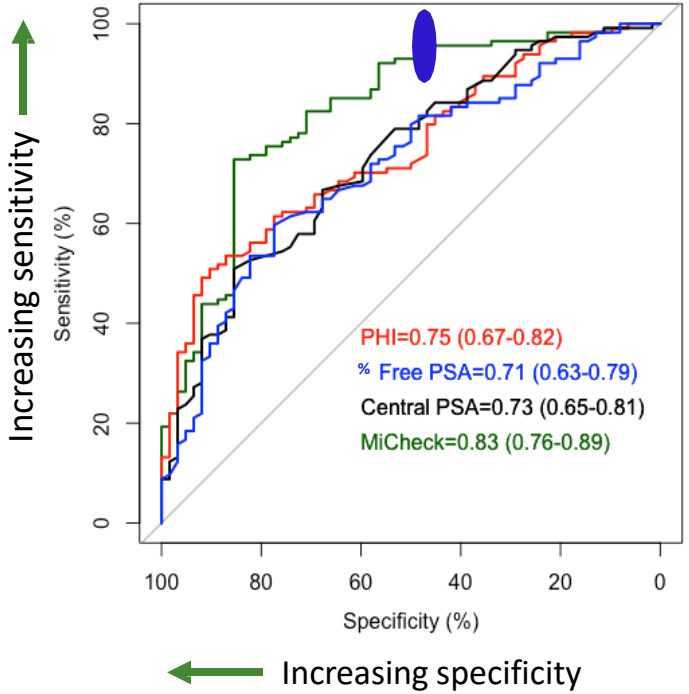
  Group C: 117 patients (37%), GS ≥ 3+4, CaP
- Serum + plasma samples collected
- Standardized PSA test + centralized pathology review by Dr Scott Lucia (both Gleason and ISUP scores)
- Algorithm developed for differentiation of aggressive (GS ≥ 3+4) v non-aggressive cancer (GS=3+3)/ no cancer

Large Urology Group Practice Association, Inc.
LUGPA

Past President
Neal D. Shore, MD, FACS
Myrtle Beach, SC

Study designed by Minomic and its International clinical advisory panel

Key MiCheck® Prostate Test Outcomes



- ✓ Highest AUC when directly compared to PSA, PHI and % free PSA
- ✓ Best test specificity at an extremely high test sensitivity (95%)
- ✓ Results in 43% fewer unnecessary biopsies
- ✓ High Negative Predictive Value (97%)

- MiCheck® has demonstrated ability to differentiate aggressive from non-aggressive cancer and no cancer
- MiCheck® demonstrates a compelling advantage in specificity over existing products shown here
- The other test's lack of specificity has led to criticism due to the resulting unnecessary biopsies – clinicians uniformly desire high specificity
- The MiCheck® technology helps fill this substantial unmet clinical need by allowing a reduction in number of biopsies

When finding aggressive cancer MiCheck® wins hands down