PSA Screening in 2024

Gerald Andriole, MD

Chief Medical Officer

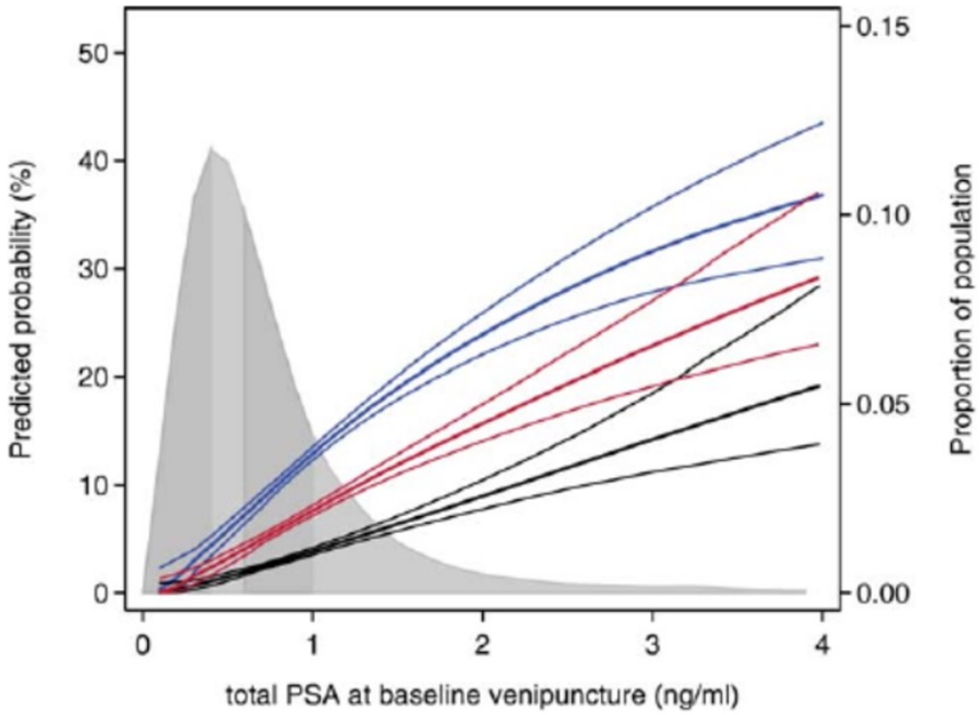
Prostatype Genomics

How to Improve Screening for CaP

1. Better Identify which men are at **above average** risk.
2. Patients and Primary Care Physicians (PCPs) need a simple message on PSA
3. Identify patients with clinically significant PCa earlier
4. Reduce unnecessary initial and repeat prostate biopsies
5. Enhance risk stratification: Better Selection for Surveillance vs. Interventional Therapy

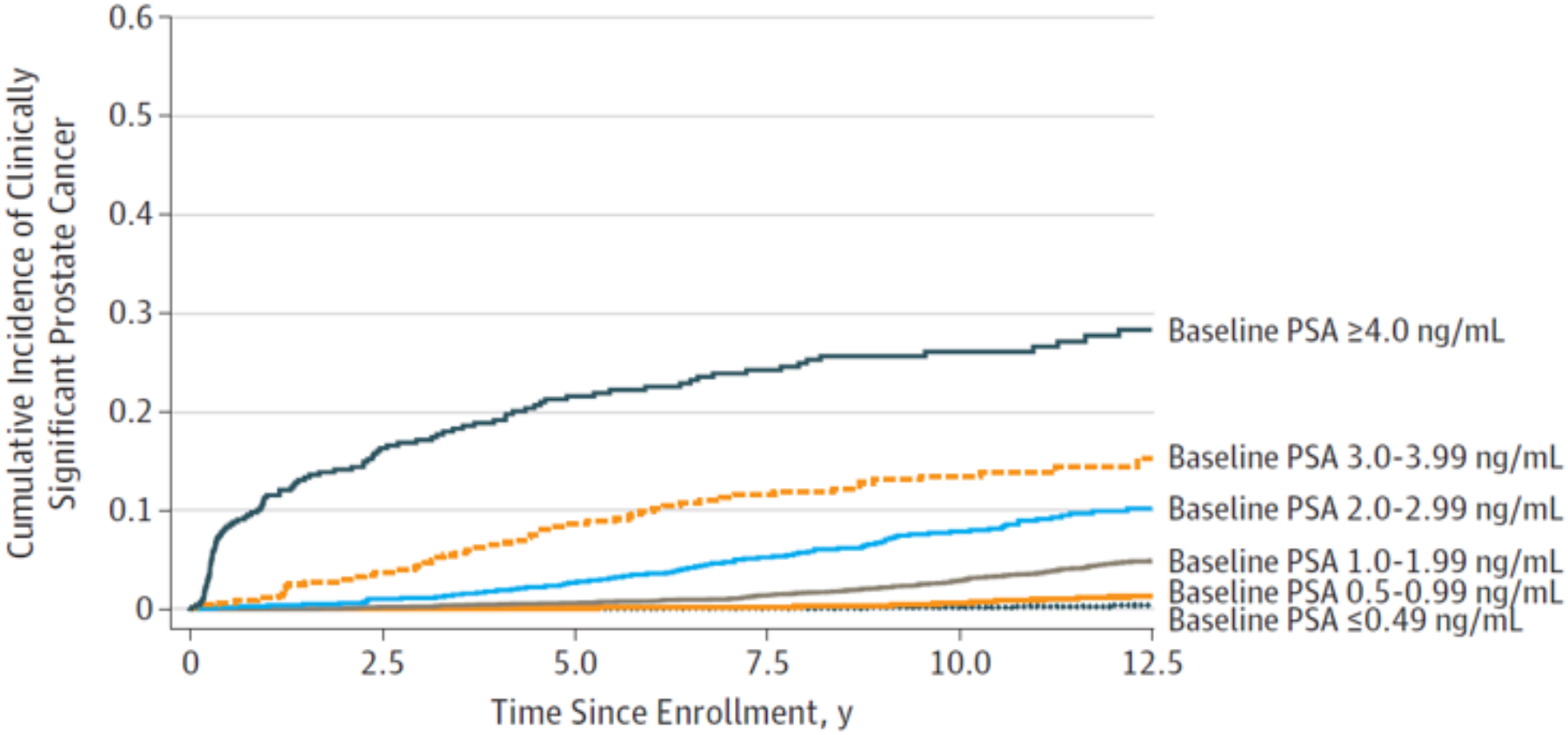
Early in Life PSA

[f] The median PSA values for men aged 40–49 years range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.



Association of Baseline Prostate-Specific Antigen Level With Long-term Diagnosis of Clinically Significant Prostate Cancer Among Patients Aged 55 to 60 Years

A Secondary Analysis of a Cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial



JAMA Network Open. 2020;3(1):e1919284. doi:10.1001/jamanetworkopen.2019.19284

CaP Risk Assessment: Early in Life PSA

- PROBASE Study
  - **PRO**state Cancer Early Detection Based on a **BASE**line PSA in Young Men
  - PSA @ age 40-45 v. start screening at 50
    - 23,301 men in early arm
      - 89% Low (PSA<1.5): get q. 5 yr PSA
      - 9% Mid (PSA 1.5-2.99): get q. 2 yr PSA
      - 1% High (PSA≥ 3) : get immediate MRI and Bx
    - 0.19% found to have CaP so far

Received: 23 July 2021 | Revised: 6 December 2021 | Accepted: 21 December 2021

DOI: 10.1002/ijc.33940

CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER UICC

Impact of Family History on CaP

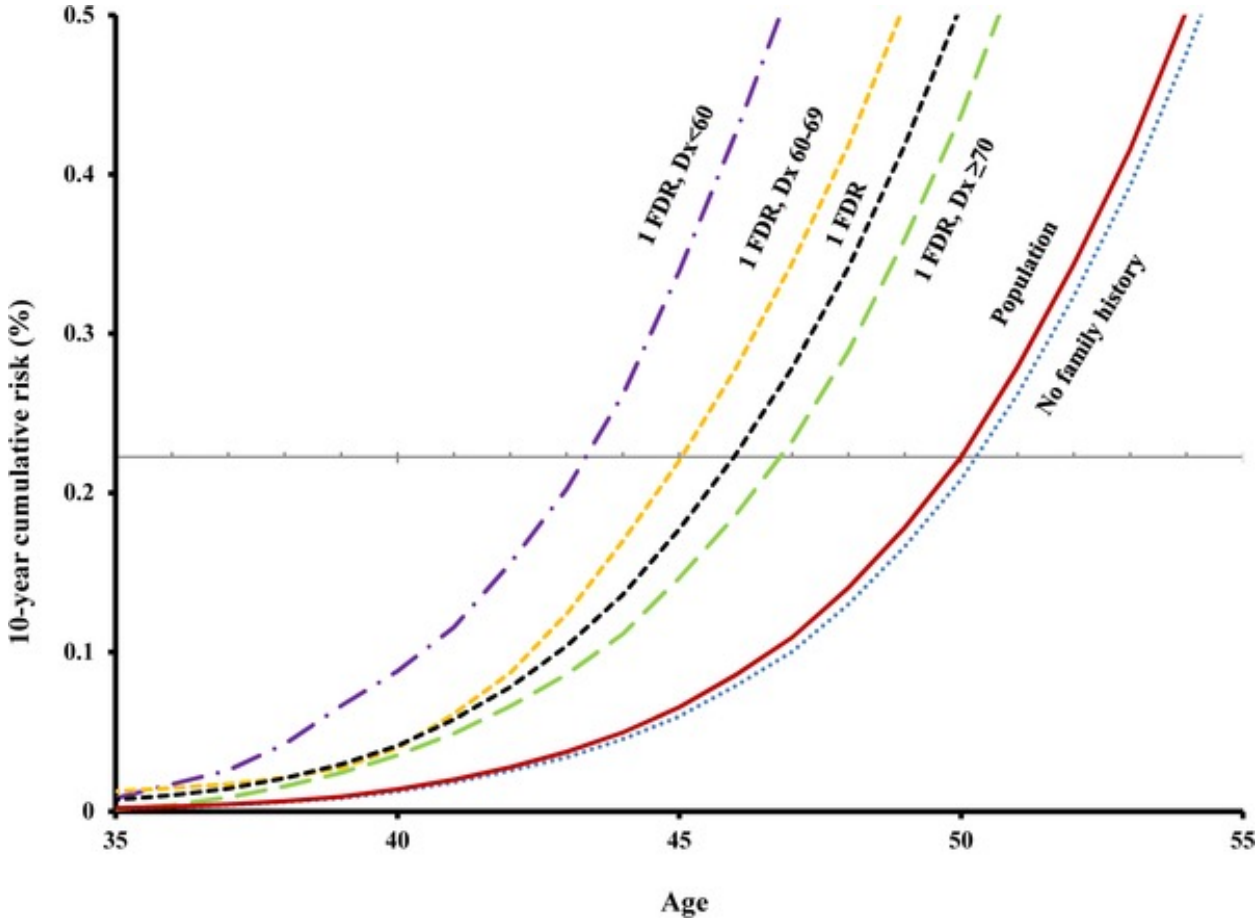
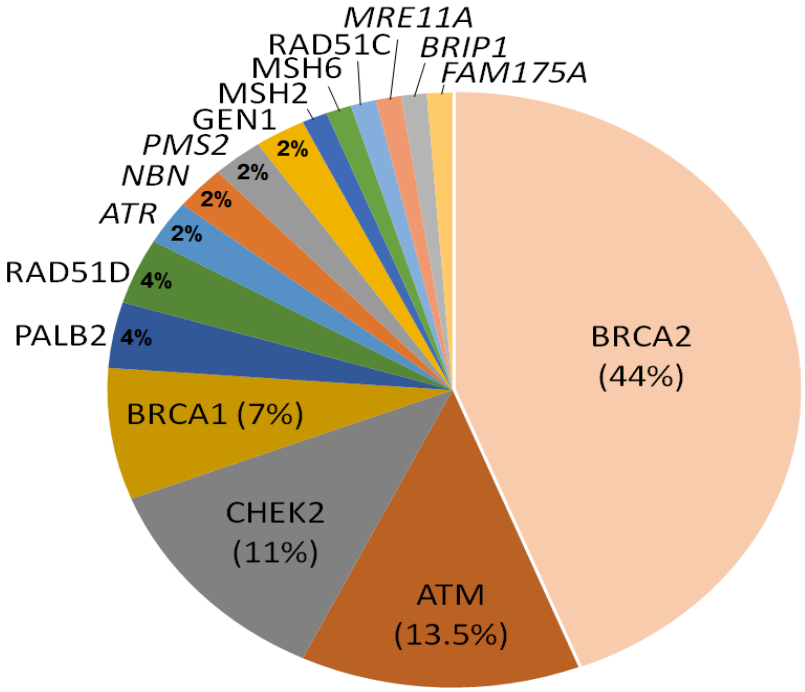


Fig 1. Age-specific 10-year cumulative risk of stage III/IV PCa or fatal PCa by age at diagnosis of invasive PCa in the affected FDR.

Xu X, Kharazmi E, Tian Y, Mukama T, Sundquist K, et al. (2021) Risk of prostate cancer in relatives of prostate cancer patients in Sweden: A nationwide cohort study. PLOS Medicine 18(6): e1003616. https://doi.org/10.1371/journal.pmed.1003616
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003616

Hereditary Risk for CaP

- BRCA-2 best studied for potential screening and treatment
- PCa males with BRCA-2 have more aggressive disease
- More work is needed on the other PCa genes identified
- Germline mutations in 11.8% of metastatic vs. 4.6% localized disease
- Later studies indicate this may be up to 25% of mCRPC



Pritchard, N Engl J Med. 2016 Aug 4;375(5):443-53; Cindamore A, Future Oncology VOL. 16, NO. 5 Online:9 Jan 2020

Genetic Change Associated with Prostate Cancer[20]

Low Penetrance Germline Genetic Testing: Role for Risk Stratification in Prostate Cancer Screening and Examples From Clinical Practice

Franklin Gaylis, MBBCh,[1-3] Kelly K. Bree, MD,[4] Paul Dato, MD,[2] Gerald L. Andriole, MD,[3,5] Christopher J. Kane, MD,[3,6] A. Karim Kader, MD, PhD[1,3]

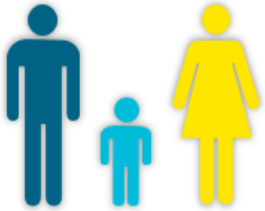
Somatic DNA
Non-Heritable

Somatic Mutation
(High Penetrant)

- Rare genetic change occurring in tumor at organ site, in this case prostate causing malignancy or progression of disease[20]
- Not passed down from parents [20]
- Only detectable in tumor containing tissue [20]

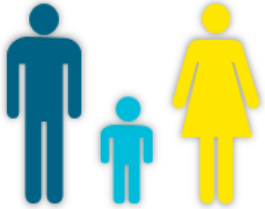
VS

Germline DNA
Heritable



Germline Mutation
(High Penetrant)

- Rare genetic change (<3%), resulting in altered biologic function [20]
- Usually passed down from one parent and is thus FH dependent [20]
- Detectable in all cells in the body [20]

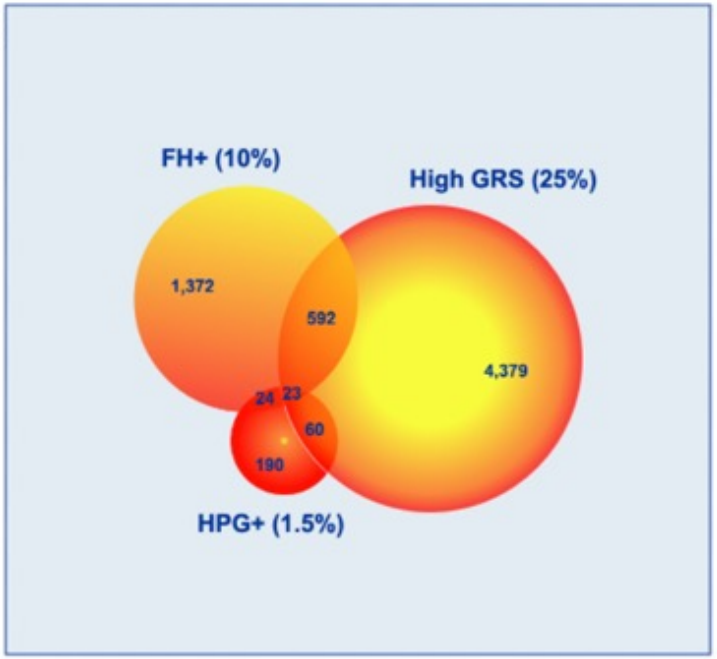


Germline SNPs
(Low Penetrant)

- Genetic change occurring in 100% of people [20]
- Get one copy of each SNP from each parent, therefore, although heritable is independent of FH [20]
- Detectable in all cells in the body [20]

Performance of Three Inherited Risk Measures for Predicting Prostate Cancer Incidence and Mortality: A Population-based Prospective Analysis

A



B

	# (%) of men	Rate/100,000 person-years		Rate Ratio	
		Incidence	Mortality	Incidence	Mortality
All subjects	20361 (100)	375	18	1	1
FH+	2,011 (10)	679	28	1.81	1.56
RPMs+	297 (1.5)	1016	39	2.71	2.14
High GRS	5,054 (25)	658	36	1.75	2.01
FH+ or RPMs+	2,261 (11)	698	30	1.86	1.66
High GRS only	4,379 (22)	585	34	1.56	1.88
Any of three	6,640 (33)	624	33	1.66	1.81
All three	23 (0.11)	2,232	0	5.95	0
FH-	18,350 (90)	342	17	0.91	0.93
RPMs-	20,064 (99)	366	18	0.98	0.98
Low GRS	5,108 (25)	183	7	0.49	0.37
None of three	13,721 (67)	256	11	0.68	0.60

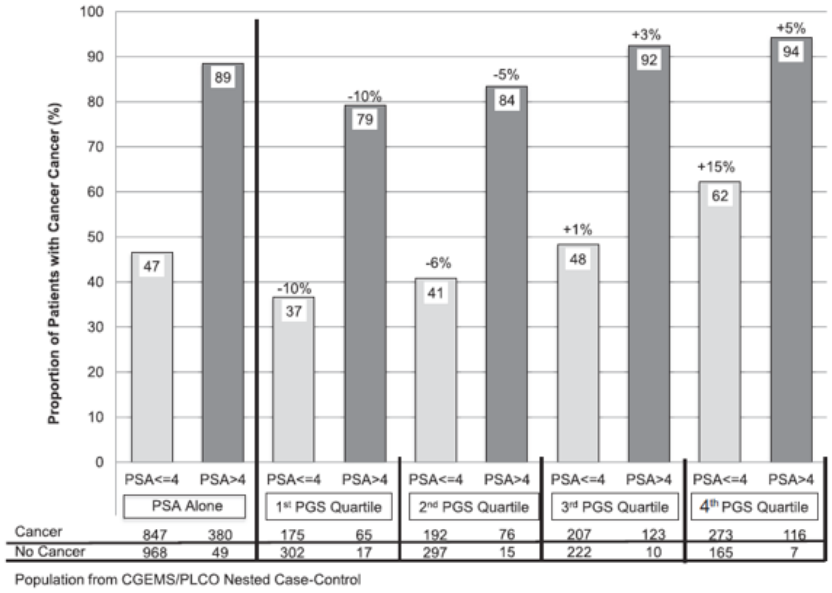
RPM: Rare Pathogenic Mutation
HPG: High Penetrance Gene
GRS: Genomic Risk Score (aka PRS-Polygenomic Risk Score)

Please cite this article in press as: Shi Z, et al. Performance of Three Inherited Risk Measures for Predicting Prostate Cancer Incidence and Mortality: A Population-based Prospective Analysis. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.11.014

Prompt – PGS Improves PSA Performance Data from the PLCO Trial[4]

Methods:

- Obtained the genetic data from the Cancer Genetic Markers of Susceptibility (CGEMS), a **nested case control study** examining germ-line DNA in the screened arm of the PLCO trial.
  - 2329 Caucasian and non-Hispanic men
  - No prior history of PCa before randomization into the trial
  - Had at least 1 PLCO PCa screen (PSA testing)
  - Controls had to have returned at least 1 annual study update



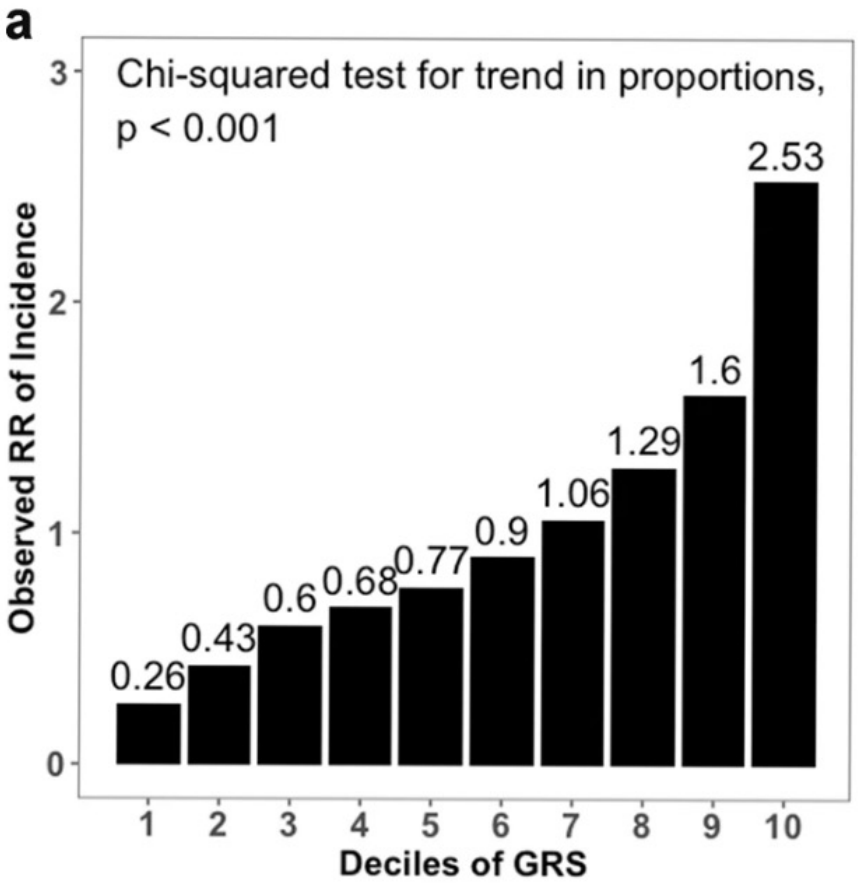
CONCLUSION

- **Germline DNA in the form of a genetic score (PGS-33) can stratify men regarding their risk of PCa.**
- **The PGS-33 may have implications regarding who may benefit most from PSA based PCa screening**

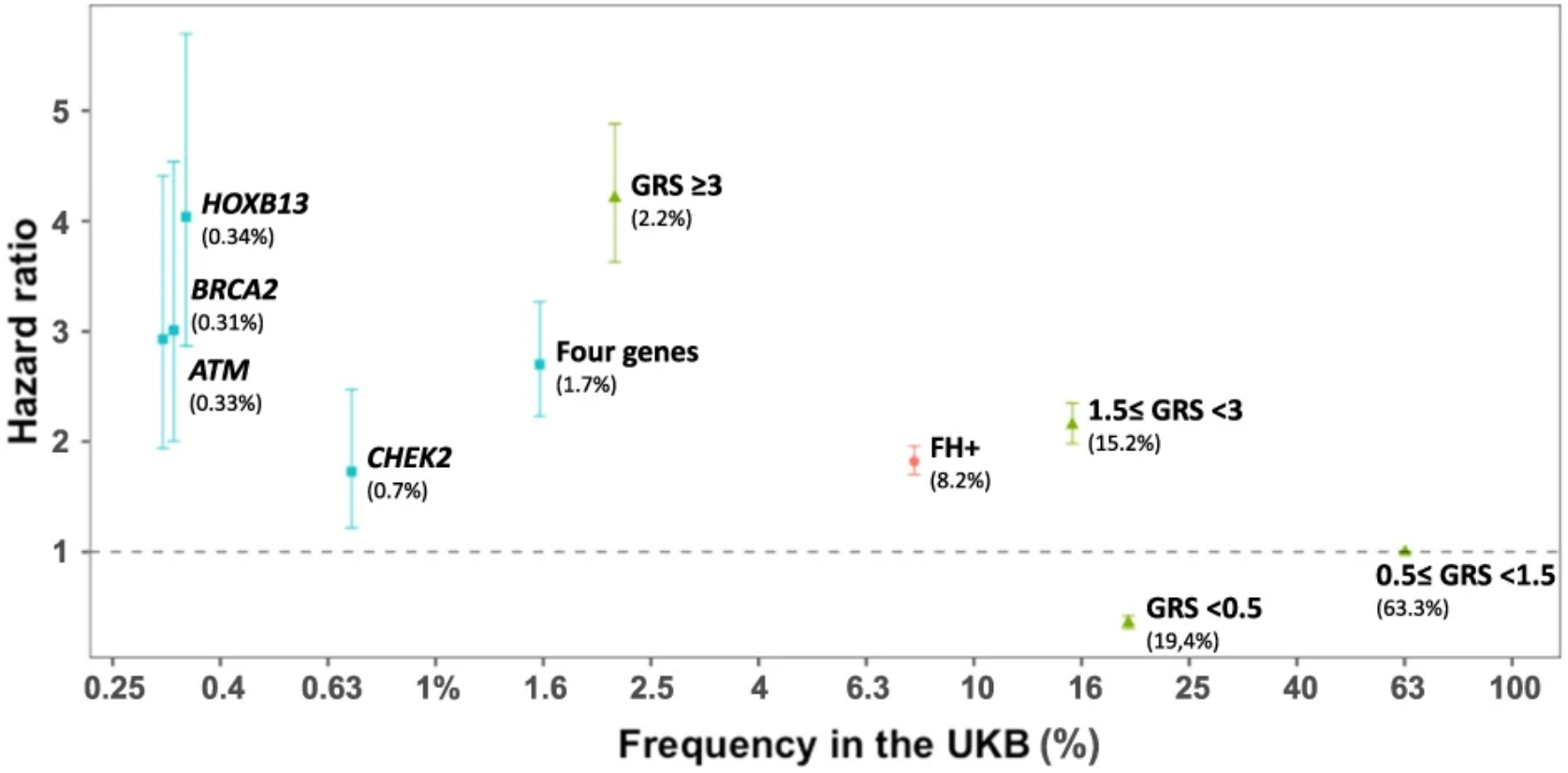
Prostate: 75:1322, 2015

UK Biobank

Xu, J., Resurreccion, W.K., Shi, Z. *et al.* Inherited risk assessment and its clinical utility for predicting prostate cancer from diagnostic prostate biopsies. *Prostate Cancer Prostatic Dis* (2022). https://doi.org/10.1038/s41391-021-00458-6



Relative Frequency and Implications of Inherited Risk Measures



Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-021-00458-6

Which SNP's Predict Aggressive Cancer?

KLK3 SNP–SNP interactions for prediction of prostate cancer aggressiveness

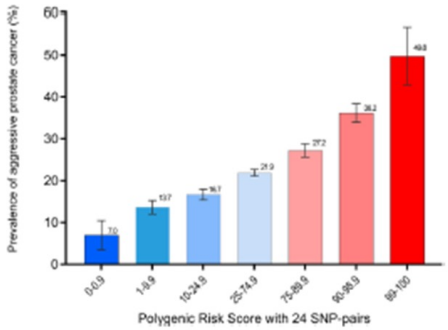
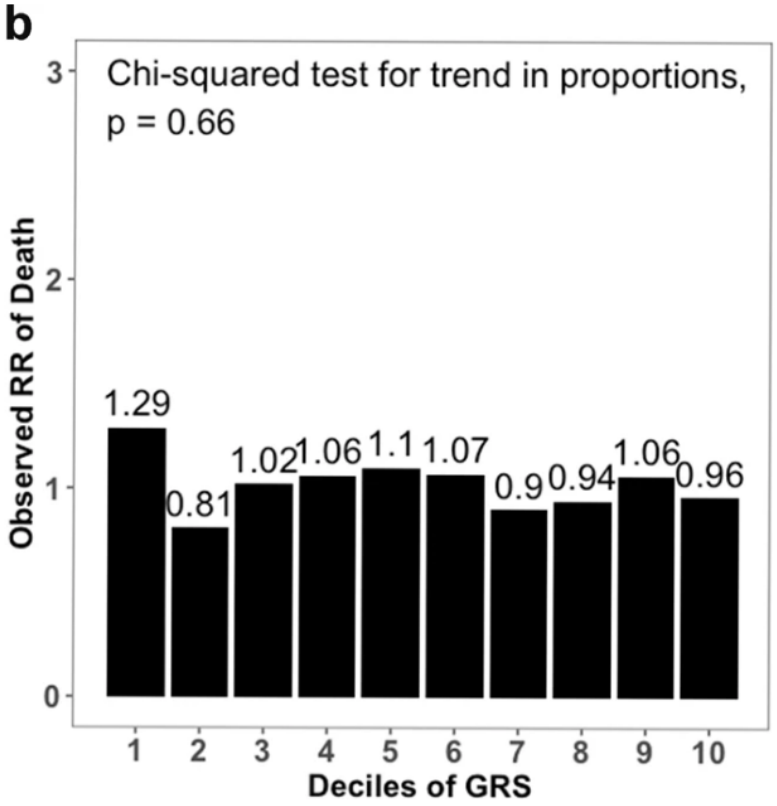


Figure 4. Performance of the polygenic risk score of prostate cancer aggresstveness based on the 24 SNP pairs. *PCa* prostate cancer, *SNP* single-nucleotide polymorphism. Mean and 95% confidence intervals of PCa aggressiveness prevalence were shown.

Scientific Reports | (2021) 11:9264 | https://doi.org/10.1038/s41598-021-85169-7



Million Veteran Program

- 590,750 Men evaluated with PHS290
- Men in top 20%-ile v. lowest 20%-ile:
  - Fatal CaP: HR 4.42 (3.91-5.02)

Harrell's concordance index (95% confidence interval) for 3 prostate cancer clinical endpoints using race and ethnicity and family history, with or without PHS290[a]

Clinical endpoints	Race and ethnicity and family history	Race and ethnicity and family history and PHS290
Fatal prostate cancer	0.597 (0.579 to 0.618)	0.701 (0.684 to 0.721)
Metastatic prostate cancer	0.595 (0.587 to 0.606)	0.693 (0.684 to 0.703)
Prostate cancer	0.583 (0.581 to 0.586)	0.688 (0.685 to 0.690)

JNCI: Journal of the National Cancer Institute, Volume 115, Issue 2, February 2023, Pages 190–199, https://doi.org/10.1093/jnci/djac199

The Prostate Cancer, Genetic Risk, and Equitable Screening Study (ProGRESS)

ClinicalTrials.gov ID NCT05926102

Sponsor VA Office of Research and Development

Design

1. Develop a precision prostate cancer screening intervention consisting of genetic testing for rare variants and a transancestry PRS, delivered to participants and their primary care providers along with individualized, genetic risk-informed screening recommendations.
2. Determine the feasibility of enrolling men aged 55-70 (35% of whom are of racial/ethnic minority groups) to a pragmatic randomized clinical trial (RCT) comparing the precision screening intervention to usual care.
3. Perform an interim assessment to determine whether the observed trajectory of prostate biopsy event rates is consistent with rates needed to detect a meaningful between-group difference at the end of the 7-year project period.

Endpoints

1. Compared with men in the usual care arm, men in the precision screening arm will have a time-to-diagnosis of clinically significant prostate cancer (csPCa, defined as NCCN classification intermediate risk or higher) that is not inferior by a margin of >30 days over a median 4 years of follow-up.

   a. If non-inferiority is demonstrated, the investigators will sequentially test the hypothesis that time-to-diagnosis of csPCa is shorter in the precision screening arm than in the usual care arm (superiority).

2. Compared with usual care, men in the precision screening arm overall will undergo fewer prostate biopsies over a median 4 years of follow-up.

Interaction of PSAD and MRI Findings

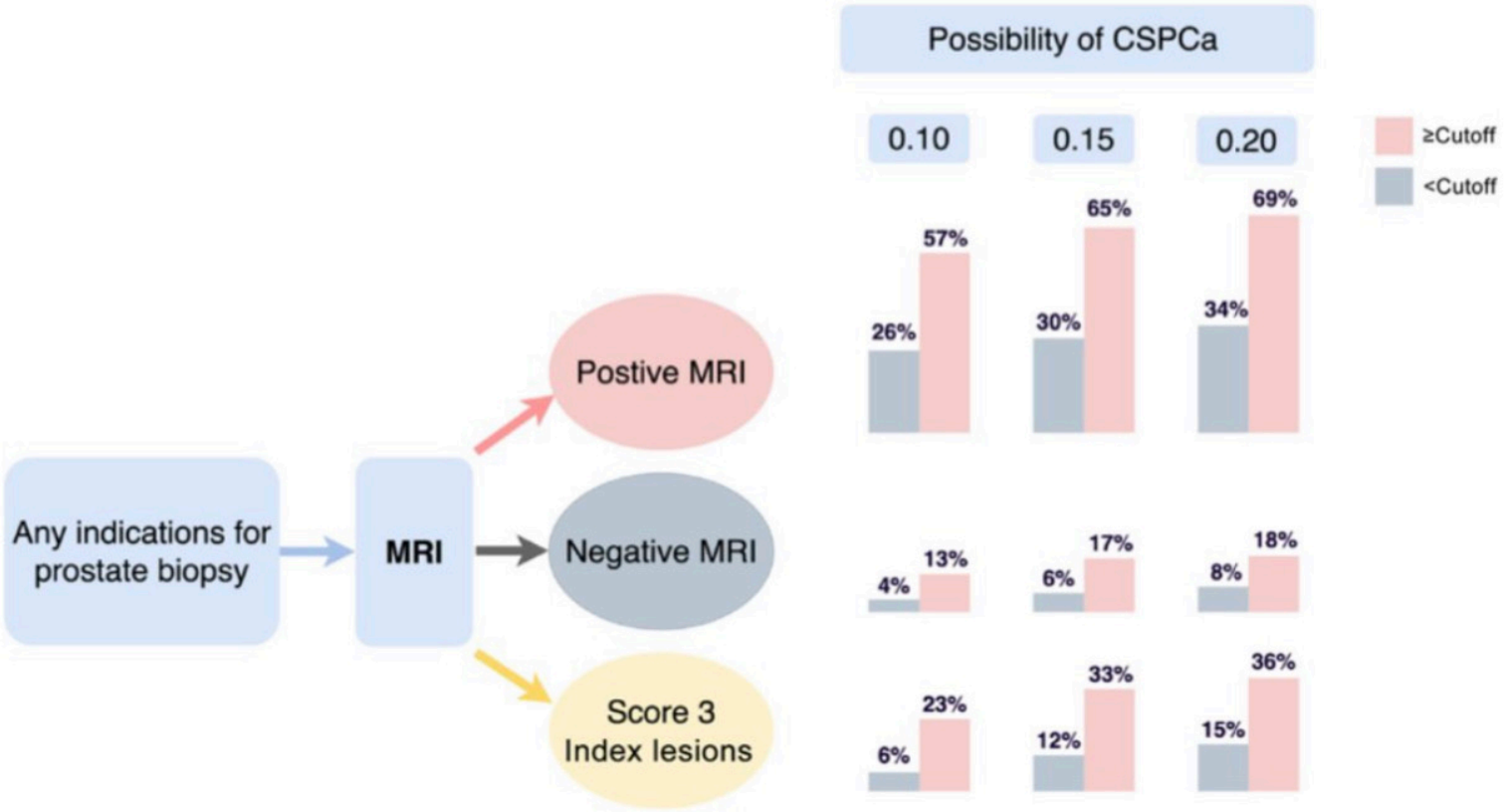


Fig. 4 – Diagnostic performance of PSAD at different cutoffs and post-test probabilities for the prediction of CSPCa. Columns and percentages represent the possibility of having CSPCa at each PSAD cutoff (0.1, 0.1,5 and 0.20 ng/ml/ml). CSPCa = clinically significant prostate cancer; MRI = magnetic resonance imaging; PSAD = prostate-specific antigen density.

August 26, 2023 • DOI: https://doi.org/10.1016/j.euo.2023.08.002

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer Early Detection

NCCN Guidelines Index
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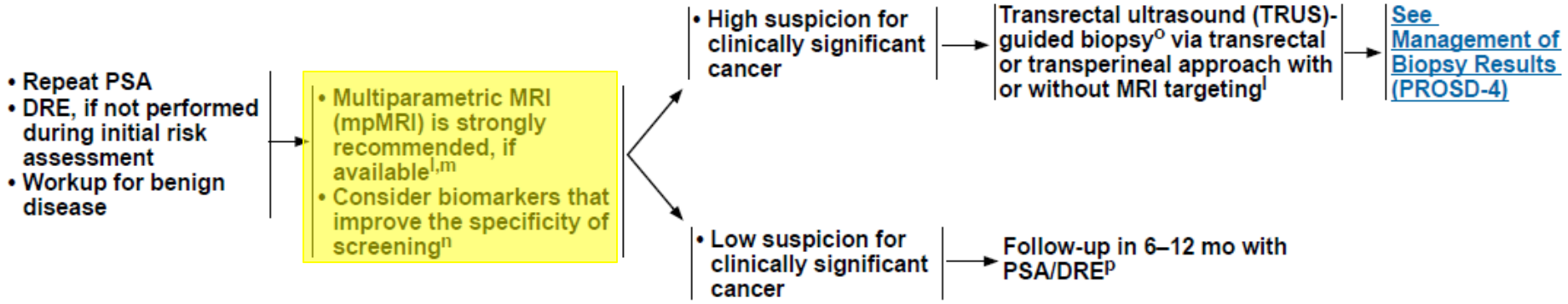
Discussion

FURTHER EVALUATION AND INDICATIONS FOR BIOPSY[k]

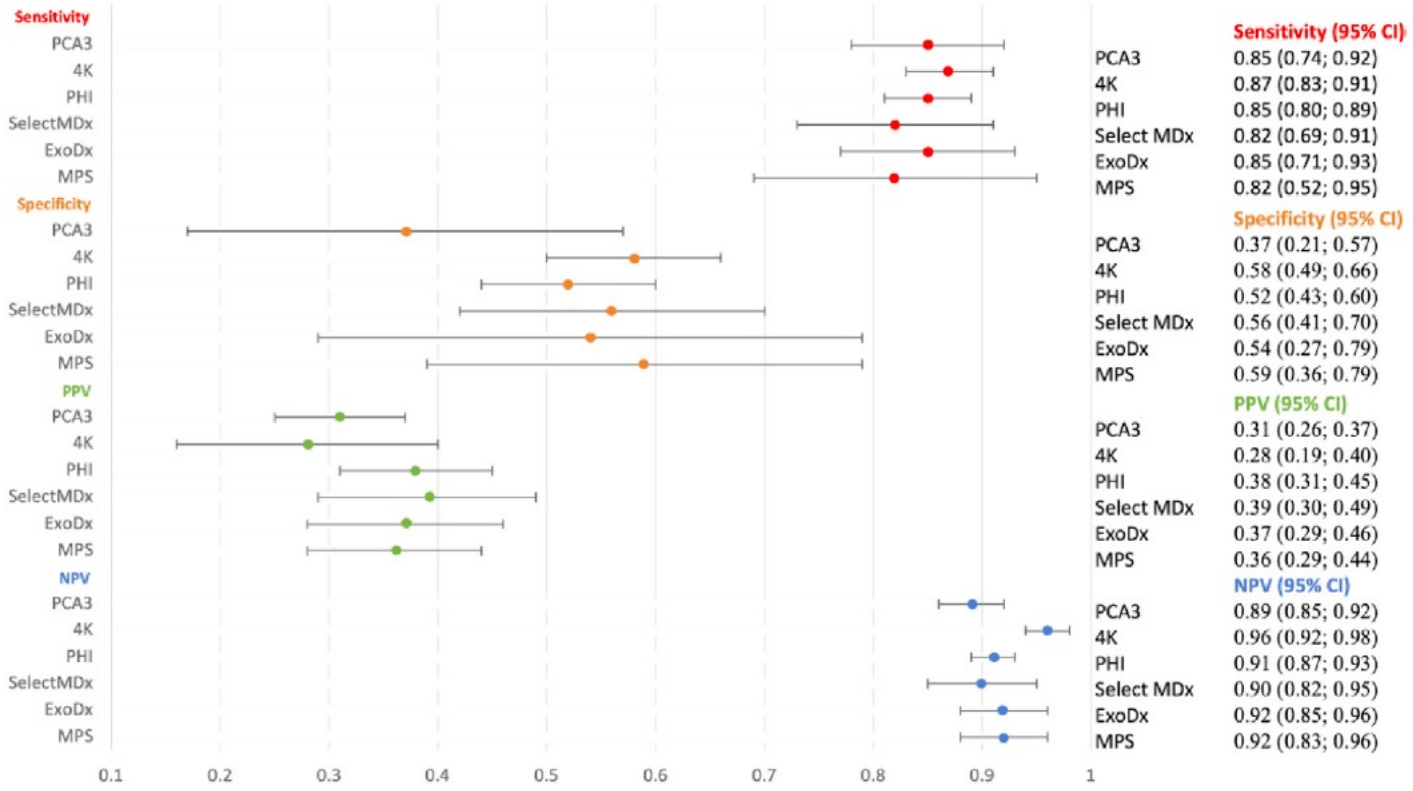
MANAGEMENT



Biomarkers to decide if a Biopsy is necessary (NCCN)

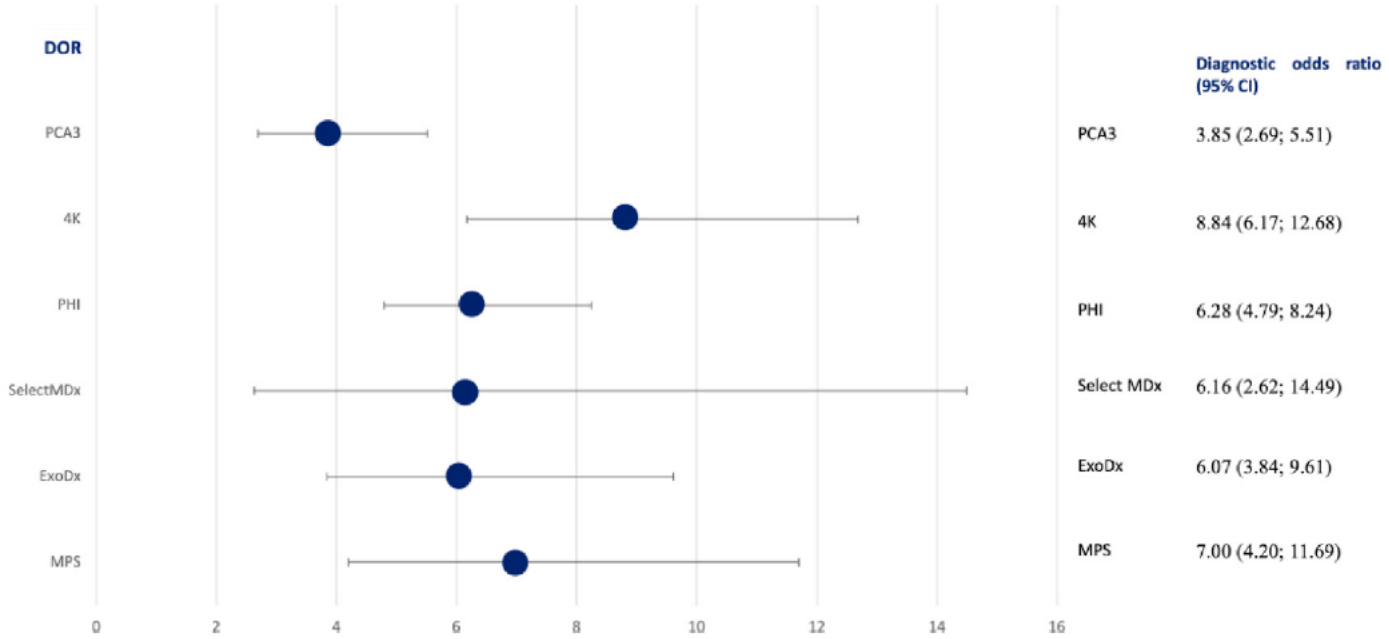
- Free PSA (Blood)
- ExoDx (Urine)
- PHI (Blood)
- OPKO 4K (Blood)
- PCA3 (Urine)
- SELECT MDx (Urine)

Biomarker Comparison



Please cite this article as: T. Kawada, S.R. Shim, F. Quhal et al., Diagnostic Accuracy of Liquid Biomarkers for Clinically Significant Prostate Cancer Detection: A Systematic Review and Diagnostic Meta-analysis of Multiple Thresholds, Eur Urol Oncol (2023), https://doi.org/10.1016/j.euo.2023.10.029

Biomarker Comparison



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Biomarker Comparison

Table 3 – Sensitivity and specificity for multiple thresholds[a]

	Biomarker	Optimal threshold	Sensitivity	Specificity
Detecting csPCa	PCA3	50.4	0.620 (0.555–0.680)	0.688 (0.632–0.739)
	4K	19.8	0.771 (0.668–0.849)	0.704 (0.620–0.777)
	PHI	44.2	0.691 (0.612–0.760)	0.715 (0.638–0.781)

csPCa = clinically significant prostate cancer.
[a] Linear mixed-effect models using different random intercepts and common random slope, b0s = b1s = bs.

Conclusions: Regarding the detection of csPCa, 4K had the highest diagnostic performance among the commercial liquid biomarkers. Based on the optimal thresholds calculated by the present meta-analysis, 4K had the highest sensitivity and PHI had the highest specificity for detecting csPCa. Nevertheless, clinical decision-making requires combination strategies between liquid and imaging biomarkers.

Please cite this article as: T. Kawada, S.R. Shim, F. Quhal et al., Diagnostic Accuracy of Liquid Biomarkers for Clinically Significant Prostate Cancer Detection: A Systematic Review and Diagnostic Meta-analysis of Multiple Thresholds, Eur Urol Oncol (2023), https://doi.org/10.1016/j.euo.2023.10.029

ProScreen Study

- Population-based randomized screening trial
- Combines PSA, 4Kscore and prostate MRI.
- 67,000 men aged 50–63 years
  - 3:1 randomization intervention:control arm
  - Screening interval is 2 years if screen-positive/Bx. Neg; 4 years if baseline PSA>1 ng/mL, and 6 years if PSA <1 ng/mL.
- Main endpoint: PCSM at 15 years, powered for ≥22% Reduction
- Approx. 60,780 currently in first screening round

BJU Int 2022; **130:** 193–199 doi:10.1111/bju.15683

Original Article

BJUI
BJU International

Population-based randomized trial of screening for clinically significant prostate cancer ProScreen: a pilot study

Some Additional Interesting Papers Published in 2023

Stockholm-3 Test

Table 2 – Head-to-head evaluation of biopsies saved and cancer cases missed using different strategies and Stockholm3 cutoffs

Strategy	Biopsies, *n* (%)		Any prostate cancer, *n* (%)			csPCa, *n* (%)		
	Performed	Saved	Found	Missed	RINB (%)	Found	Missed	RINB (%)
Biopsy all	342 (100)	–	201 (100)	–	–	154 (100)	–	–
Stockholm3 ≥11%	269 (79)	73 (21)	178 (89)	23 (11)	32	142 (92)	12 (8)	16
Stockholm3 ≥11% + PV + DRE	251 (73)	91 (27)	173 (86)	28 (14)	31	139 (90)	15 (10)	16
Stockholm3 ≥15%	232 (68)	110 (32)	165 (82)	36 (18)	33	133 (86)	21 (14)	19
PSAD ≥0.15 ng/ml^2	160 (47)	182 (53)	123 (61)	78 (39)	43	106 (69)	48 (31)	26
Stockholm3 ≥11% + PI-RADS ≥3	244 (73)	92 (27)	167 (83)	34 (17)	37	135 (87)	19 (14)	21
Stockholm3 ≥15% + PI-RADS ≥3	211 (63)	125 (37)	165 (82)	36 (18)	29	134 (87)	20 (15)	16
PSAD ≥0.15 and PI-RADS ≥ 3	138 (41)	198 (59)	110 (55)	91 (45)	46	95 (62)	59 (38)	30

PV = prostate volume; DRE = digital rectal examination; PSAD = prostate-specific antigen density; RINB = risk if no biopsy performed; csPCa = clinically significant prostate cancer (International Society of Urological Pathology grade group ≥2); PI-RADS = Prostate Imaging-Reporting and Data System.

Please cite this article as: A. Elyan, K. Saba, A. Sigle et al., Prospective Multicenter Validation of the Stockholm3 Test in a Central European Cohort, Eur Urol Focus (2023), https://doi.org/10.1016/j.euf.2023.09.016

Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

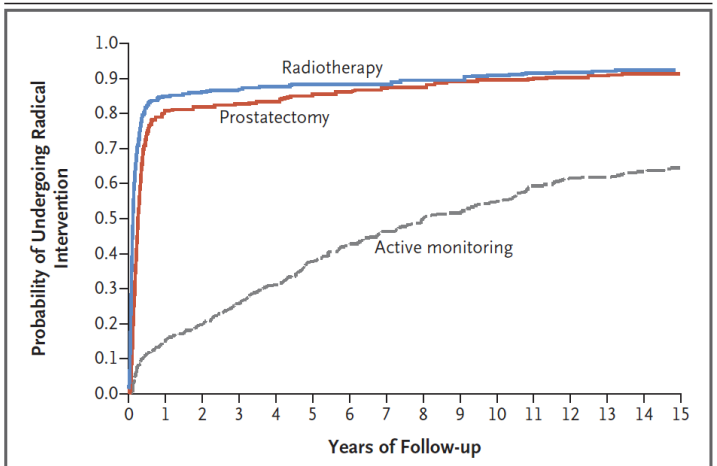


Figure 3. Probability of Undergoing Radical Intervention during the Follow-up Period.

Shown are Kaplan–Meier estimates of the cumulative probability that trial patients would undergo a radical intervention — prostatectomy, radiotherapy, or other intervention — during the follow-up period, according to trial-group assignment at the time of diagnosis.

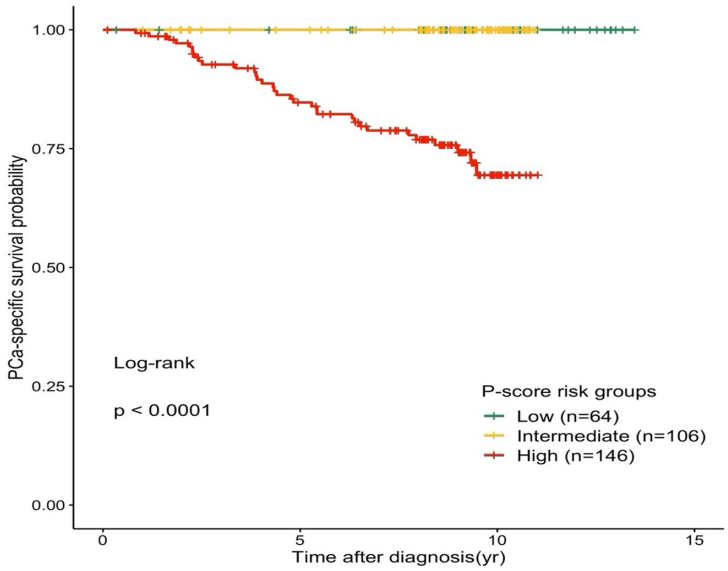
Table 1. Primary and Secondary Outcomes.

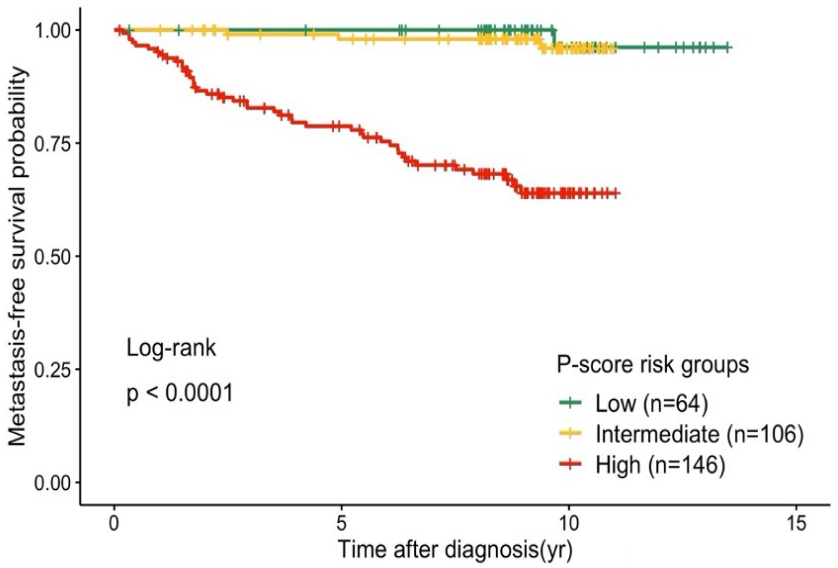
Outcome and Trial Group	No. of Events	No. of Person-Yr	Rate per 1000 Person-Yr (95% CI)	Hazard Ratio (95% CI)*
Primary outcome				
Death from prostate cancer†				
Active monitoring	17	7633	2.2 (1.4–3.6)	Reference
Prostatectomy	12	7766	1.5 (0.9–2.7)	0.66 (0.31–1.39)
Radiotherapy	16	7628	2.1 (1.3–3.4)	0.88 (0.44–1.74)
Secondary outcomes				
Death from any cause				
Active monitoring	124	7633	16.2 (13.6–19.3)	Reference
Prostatectomy	117	7766	15.0 (12.5–18.0)	0.89 (0.69–1.15)
Radiotherapy	115	7628	15.0 (12.5–18.0)	0.88 (0.68–1.13)
Metastatic disease				
Active monitoring	51	7324	7.1 (5.4–9.3)	Reference
Prostatectomy	26	7594	3.5 (2.4–5.1)	0.47 (0.29–0.76)
Radiotherapy	27	7467	3.7 (2.5–5.4)	0.48 (0.30–0.77)
Androgen-deprivation therapy				
Active monitoring	69	7197	9.4 (7.4–11.9)	Reference
Prostatectomy	40	7452	5.3 (3.9–7.2)	0.54 (0.37–0.80)
Radiotherapy	42	7328	5.6 (4.2–7.6)	0.54 (0.36–0.79)
Clinical progression‡				
Active monitoring	141	6596	21.4 (18.1–25.2)	Reference
Prostatectomy	58	7258	8.0 (6.2–10.3)	0.36 (0.27–0.49)
Radiotherapy	60	7173	8.4 (6.5–10.8)	0.35 (0.26–0.48)

ProtecT, Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer, Hamdy et al, NEJM 2023

Prostatype® Test Uses the Expression Profiles of Three Embryonic Cancer Stem Cell Genes, PSA, T-Stage and Biopsy Gleason Score

- Prediction of 10-Yr PCSM
- Prediction of Distant Metastases





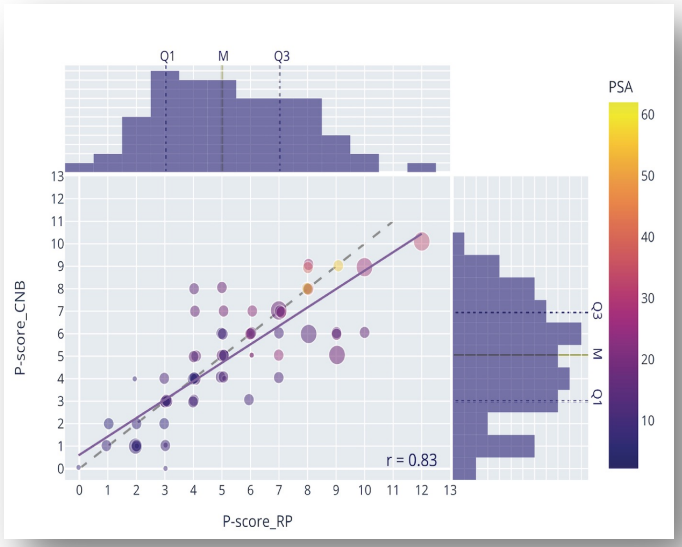
Validation of the prognostic value of a three-gene signature and clinical parameters-based risk score in prostate cancer patients. Sæmundsson et al, The Prostate 2023

www.prostatypegenomics.com

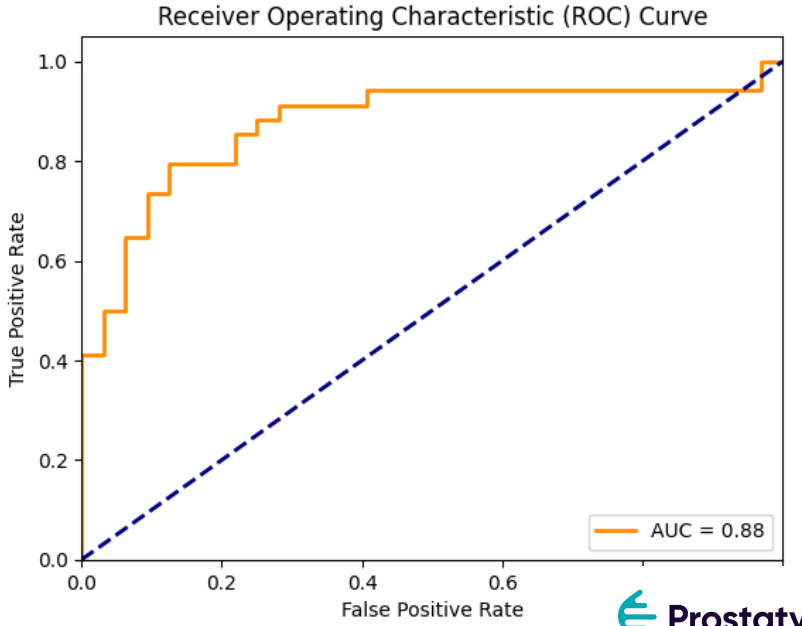
Prostatype Genomics

Prostatype® Test Uses the Expression Profiles of Three Embryonic Cancer Stem Cell Genes, PSA, T-Stage and Biopsy Gleason Score

- Concordance of paired CNB and RP



- Prediction of Adverse Pathology



Validation of the prognostic value of a three-gene signature and clinical parameters-based risk score in prostate cancer patients. Sæmundsson et al, The Prostate 2023., P-score in preoperative biopsies accurately predicts P-Score in final pathology at radical prostatectomy in patients with localized prostate cancer, Röbeck et al, The Prostate 2023 AP AUC calculated using both data sets.. Data on file. www.prostatypegenomics.com

Prostatype Genomics

Screening for Prostate Cancer

Paul F. Pinsky, Ph.D., and Howard Parnes, M.D.

N Engl J Med 2023;388:1405-14.
DOI: 10.1056/NEJMcp2209151

Consistent rec.
to test healthy
men less than 70, esp.
if they have +FH of CaP
and/or are A-A
after "Shared Decision Making"

Table 2. U.S. and Selected Other Guidelines on Screening for Prostate Cancer.*

Organization and Recommendations	Population	Screening Interval	Comment
U.S. Preventive Services Task Force[24]			
Discuss the harms and benefits of PSA screening with patient	Age 55–69 yr	Not addressed	Grade C recommendation (at least moderate certainty that the net benefit is small)
No screening	Age ≥70 yr	NA	Grade D recommendation
National Comprehensive Cancer Network[51]			
Discuss risks and benefits to early detection of prostate cancer	Average risk, age 45–75 yr; high risk, age 40–75 yr†	2–4 yr with PSA level of <1 ng/ml); 1–2 yr with PSA level of ≥1 ng/ml	
No screening	Age >75 yr	NA	
American Urological Association[29]			
Shared decision making	Age 55–69 yr	2 yr	Moderate strength of evidence
No routine screening	Age 40–54 yr or ≥70 yr	NA	Weak strength of evidence
American Academy of Family Physicians[52]			
Shared decision making	Age 55–69 yr	≥2 yr	Grade C recommendation (selective offering based on professional judgment and patient preferences)
No screening	Age ≥70 yr	NA	
American Cancer Society: discuss screening[53]	Age ≥50 yr‡; age ≥45 yr for non-Hispanic Black men or men with a first-degree relative with prostate cancer that was diagnosed by age 65 yr‡	2 yr with PSA level of <2.5 ng/ml; 1 yr with PSA level of ≥2.5 ng/ml	
EAU–EANM–ESTRO–ESUR–SIOG[56]			
Individualized, risk-adapted strategy for screening	Life expectancy at least 10–15 yr	2 yr for men at elevated risk according to PSA level and age; 8 yr for men at lower risk	Weak recommendation
No screening without counseling regarding potential risks and benefits	NA	NA	Strong recommendation
Canadian Task Force on Preventive Health Care: no screening[54]	NA	NA	Strong recommendation for men <55 yr or ≥70 yr of age; weak recommendation for men 55–69 yr of age
Japan Urological Association: screening[55]	Age ≥50 yr; age ≥40 yr with family history	3 yr with PSA level of <1 ng/ml; 1 yr with PSA level of ≥1 ng/ml	Recommendation that fact sheets be provided that include important issues regarding prostate cancer

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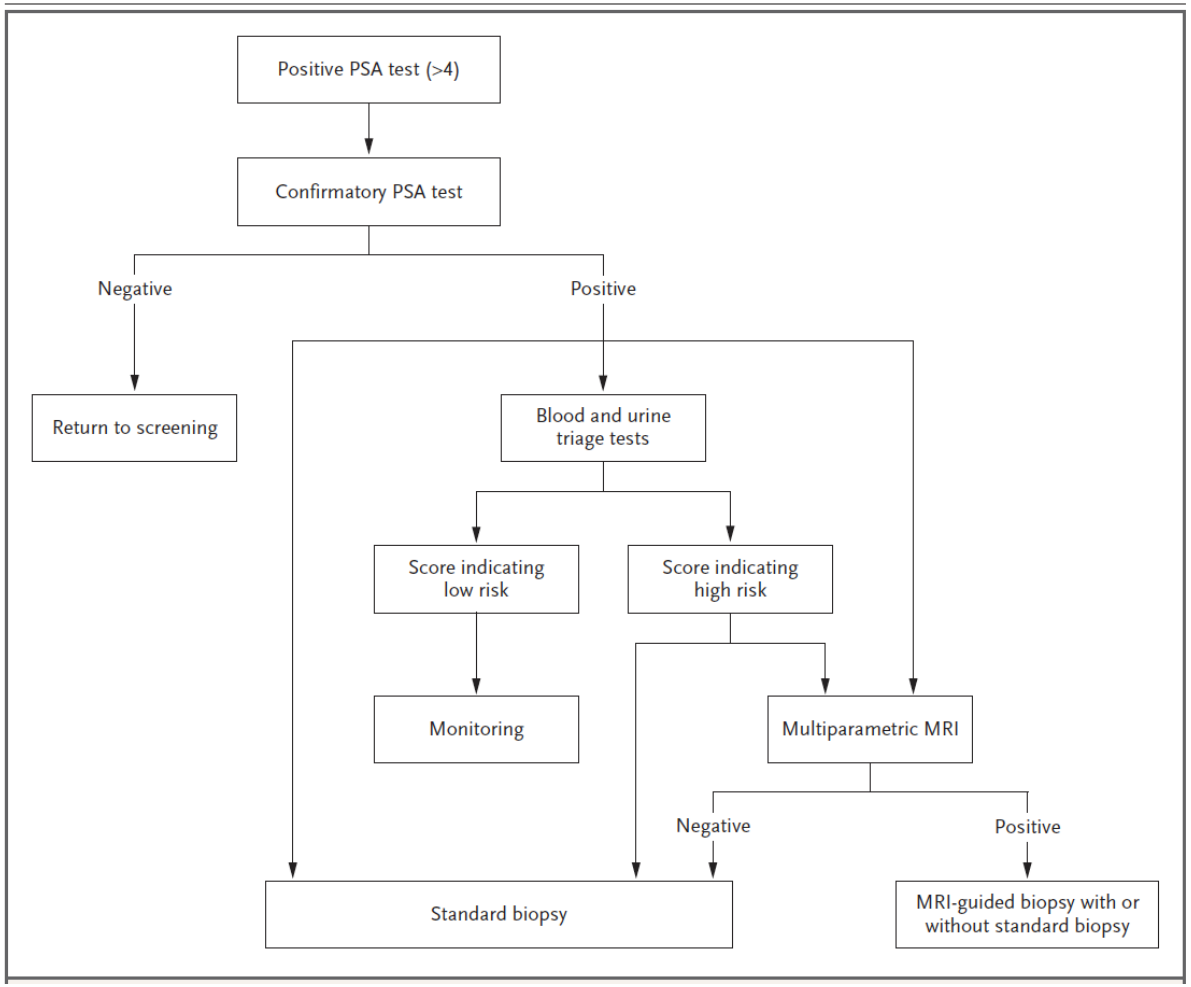
Screening for Prostate Cancer

N Engl J Med 2023;388:1405-14.
DOI: 10.1056/NEJMcp2209151

Paul F. Pinsky, Ph.D., and Howard Parnes, M.D.



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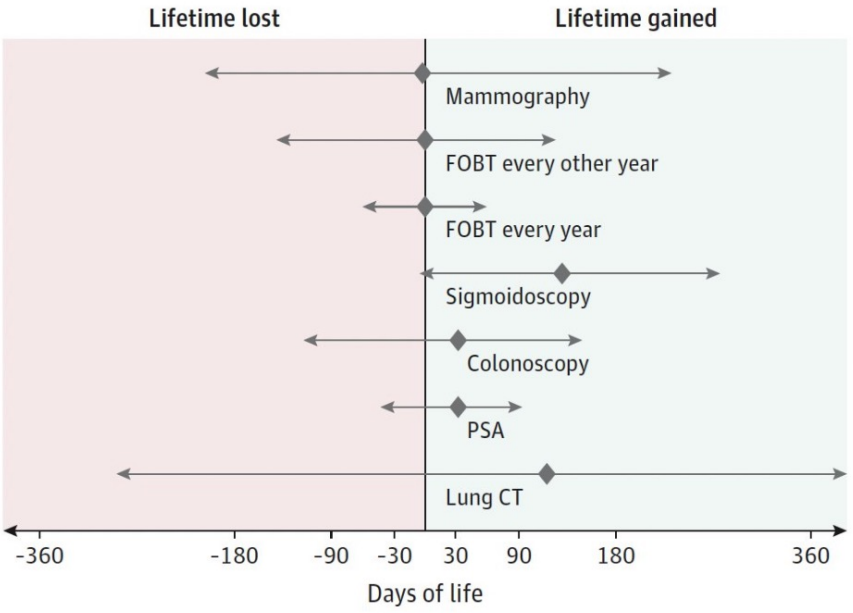
Estimated Lifetime Gained With Cancer Screening Tests

A Meta-Analysis of Randomized Clinical Trials

Figure 2. Lifetime Gained With Commonly Used Cancer Screening Tests



The diamonds indicate point estimates of life days gained or lost for each screening test. Left and right arrows indicate 95% CIs. CT indicates computed tomography; FOBT, fecal occult blood testing; and PSA, prostate-specific antigen.

August 28, 2023. doi:10.1001/jamainternmed.2023.3798

Conclusions and clinical implications: Our comprehensive review and meta-analysis indicates that both as an independent test and as a supplementary measure to PSA for PCa detection, DRE exhibits a notably low diagnostic value. The collective findings from the included studies suggest that, in the absence of clinical symptoms and signs, DRE could be potentially omitted from PCa screening and early detection strategies.

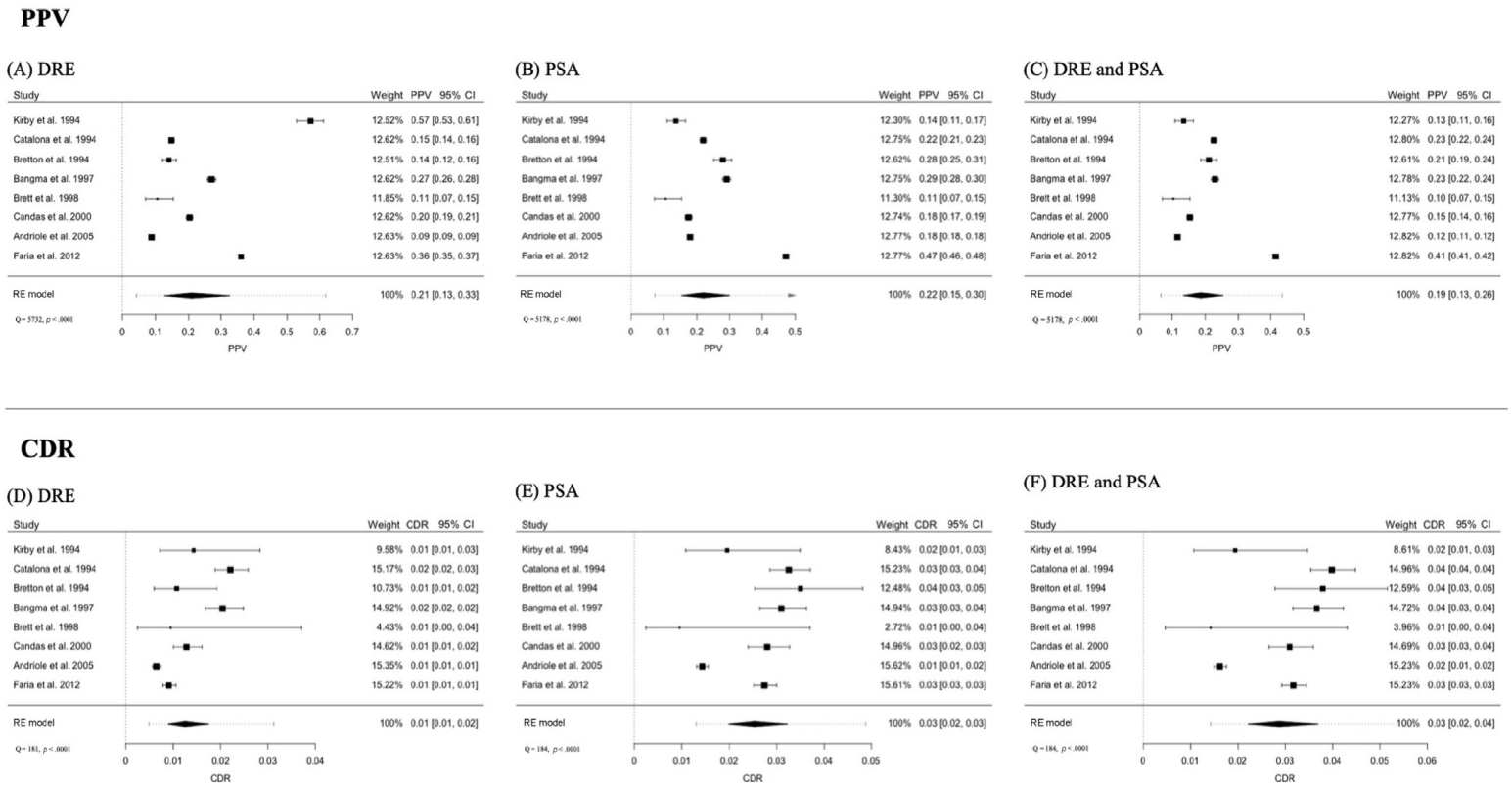


Fig. 2 – Forest plots for the PPV of (A) DRE, (B) PSA, and (C) DRE + PSA; and the CDR of (D) DRE, (E) PSA, and (F) DRE + PSA. PPV = positive predictive value; DRE = digital rectal examination; PSA = prostate-specific antigen; CDR = cancer detection rate; CI = confidence interval; RE = random effects.

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Malpractice Trends Involving Active Surveillance Across Cancers

Results: Five prostate cancer cases were identified that pertained to active surveillance. Two cases involved alleged deliberate indifference from AS as a management strategy but were ruled as following appropriate standard of care. In contrast, three cases involved alleged physician negligence for not having explicitly recommended AS as a treatment option, after complications from surgery occurred. All cases showed documented informed consent for AS, leading to defense verdicts for the physicians. No cases of AS-related malpractice were identified for other cancer types.

Ann Surg. 2023 Sep 25. doi: 10.1097/SLA.0000000000006101.

Prostate Cancer Screening: We need to do it Right!

- Aggressively screen those men who need it
  - Family Hx, Race, PSA in 40's, PGRS
- Consider lower PSA cut-point for referral for GU eval.
- Abnormal PSA should **not** result in automatic biopsy
  - Get MRI and/or Biomarker(s) (eg OPKO-4K)
- Do a "quality" biopsy if needed
  - Image-Guided
  - Avoid office-based, random transfecal biopsy
- If cancer detected, consider patient and tumor factors and possibly a genomic classifier (esp if findings are divergent) before recommending treatment