Appendix A: Search Strategies for PCA3 Testing for the Diagnosis and Management of Prostate Cancer

02/09/11

((prostate cancer antigen 3, human [SUBSTANCE NAME] OR pca3 [TIAB] OR (prostate cancer antigen 3 [TIAB]) OR (prostatic cancer antigen 3 [TIAB]) OR DD3 antigen, human [SUBSTANCE NAME] OR (differential display code 3 [TIAB]) OR dd3 [TIAB]) OR (prostatic neoplasms [MH] AND ((clinical* [TIAB] AND (significan* [TIAB] OR importan* [TIAB])) OR aggressive [TIAB] OR biops* [TIAB]) AND (nomogram [TIAB] OR (neural [TIAB] AND network [TIAB])))) OR ((((((clinical* [TIAB] AND (significan* [TIAB] OR importan* [TIAB])) OR aggressive [TIAB] OR biops* [TIAB]) AND prostate-specific antigen [MH]) AND prostatic neoplasms [MH]) AND (predict* [TIAB] OR prognos* [TIAB])))

Revised Searches (PubMed only)

"prostate cancer antigen 3, human" [Supplementary Concept] OR
("differential display code 3 antigen" OR DD3) Field: Title/Abstract OR
(PCA3 OR "prostate cancer antigen 3") Field: Title/Abstract

- This was the test-specific set= 208 in PubMed

Additionally -
"Prostatic Neoplasms"[Mesh] OR "prostatic neoplasms" OR "prostate neoplasms" OR "prostatic cancer" OR "prostate cancer"
AND
(nomogram OR (neural AND network) OR antigen OR antigens) Field: Title/Abstract
AND
((clinical* AND (significan* OR importan* OR aggressive OR biops*)) OR predict* OR prognos* OR (select* OR decid* OR decision* OR choos* OR choice*)) Field: Title/Abstract
NOT the test-specific set
AND Limits: Humans, Publication Date from 1/1/1990 to search date.

PUBMED on 8/9/11

<u>Test specific search</u>
"prostate cancer antigen 3, human" [Supplementary Concept] OR PCA3 OR DD3 OR DD3PCA3 OR "DD3(PCA3)" OR "prostate cancer gene 3" OR "prostate cancer antigen 3" OR progensa OR ("differential display code 3" AND (prostate OR prostatic))
AND
Limits: Humans, English = 159

<u>Comparators search</u>
1. <u>PSA/total PSA</u>
"Prostate-Specific Antigen"[Mesh] OR "total PSA" OR "total prostate specific antigen" OR "prostate specific antigen" OR (PSA AND (prostate OR prostatic))

AND
Publication type: meta-analysis OR Subset: systematic review OR "meta-analysis" OR metaanalysis OR "systematic review"
AND
Limits: Humans, English = 480

2. PSA velocity/free PSA/complexed PSA/externally validated nomograms
"PSA velocity" OR "prostate specific antigen velocity" OR "free PSA" OR "free prostate specific antigen" OR "complexed PSA" OR "c-PSA" OR "complexed prostate specific antigen" OR (nomogram* AND (prostatic OR prostate))
AND
Publication Types: Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study OR Subset: systematic review
AND
Limits: Humans, English = 521

EMBASE on 8/15/11

Test specific search
'prostate cancer antigen 3, human' OR pca3 OR dd3 OR dd3pca3 OR 'dd3(pca3)' OR 'prostate cancer gene 3' OR 'prostate cancer antigen 3' OR progensa OR ('differential display code 3' AND ('prostate'/exp OR prostatic))
AND
‘prostate'/exp OR prostatic
AND
Limits: Humans, English = 64

Comparators search
1. PSA/Total PSA
'total psa' OR 'total prostate specific antigen' OR 'prostate specific antigen'/exp OR (psa AND ('prostate'/exp OR prostatic))
AND
'meta analysis'/exp OR 'systematic review'/exp OR 'metaanalysis'/exp
AND
Limits: Humans, English 258

2. PSA velocity/free PSA/complexed PSA/externally validated nomograms
'psa velocity' OR 'prostate specific antigen velocity' OR 'free psa' OR 'free prostate specific antigen' OR 'complexed psa' OR 'c-psa' OR 'complexed prostate specific antigen' OR (nomogram* AND (prostatic OR 'prostate'/exp))
AND
'meta analysis'/exp OR 'systematic review'/exp OR 'metaanalysis' OR 'randomized clinical trial' OR 'randomised clinical trial' OR 'comparative trial' OR 'controlled trial'/exp OR random OR 'comparison'/exp
AND
'major clinical study'/de

AND
Limits: Humans, English =125

Cochrane Central
Test names searched for anything that was not in the other two databases' results = 2 new records

Additional comparator searching in Cochrane = 160 new records

Appendix B: Data Elements

- Study description and design, including:
  - Country, institutions and enrollment period
  - Enrollment number and flow of subjects through PCA3 and comparator testing, prostate biopsy, treatment and followup
  - Source of funding and authors' disclosures of industry relationship(s)
  - Blinding of index and comparator test results to pathologists and of biopsy/prostatectomy results to laboratorians conducting tests
- Participant characteristics, including
  - Demographics of the study population
  - Criteria for study inclusion (e.g., age, race, elevated tPSA, abnormal DRE, previous negative or positive biopsy, family history)
  - Comorbidities or potential effect modifiers
- Prostate biopsy (KQ1-3) and radical prostatectomy (KQ3) findings, including:
  - Cores per biopsy, positive cores per biopsy
  - Gleason scores
  - Other biomarkers (e.g., PSA density)
  - Pathological markers
  - Percentage of 'insignificant findings' based on identified criteria
  - Clinical and pathological staging of tumor from prostatectomy
- PCA3 specimens and assay characteristics, including:
  - Method of collection
  - Handling/storage
  - PCA3 assay used (e.g., specific test or method, housekeeping gene used, reporting unit)
- PCA3 and comparator test results, including:
  - Specified comparators were total PSA, PSA velocity or doubling time, free PSA, PSA density, complexed PSA, externally validated nomograms or risk assessment programs
  - Cutoffs/thresholds/action points
  - Summary measures (e.g., mean or median values), stratified by negative or positive biopsy result, cutoff, or other variables
- Intermediate outcomes, including:
  - Diagnostic accuracy data, including area under the ROC (receiver operating characteristics) curve (AUC), diagnostic odds ratios, clinical sensitivity and specificity, positive and negative predictive values
  - Data on decisionmaking related to biopsy, with definition of study design, description of participants and instruments used, and outcome measures
  - Data on harms related to biopsy, with definition of study design, description of participants and instruments used, and findings
- Long-term outcomes, including:
  - Mortality, including overall and prostate cancer-specific mortality and 10-year survival

    - Morbidity, including local progression, distant metastases, pain, and biochemical failure
    - Treatment-related morbidity, including urinary incontinence, impotence, rectal incontinence and prostatitis
    - Quality-of-life measures
- Statistical analyses, including:
    - Statistical tests used
    - Confidence intervals for performance estimates
    - p values for comparisons
    - Assessment of potential biases
- Quality assessment:
    - Selection of participants to avoid bias
    - Adequate descriptions of study design and process and reasons for cases lost
    - Use of blinding
    - Methods are described below in the section entitle Assessment of Methodological Quality of Individual Studies

Appendix C:
Search Strategy for the Grey Literature

Regulatory Information
FDA
Source: http://www.fda.gov/default.htm
Date searched: 8/15/2011
Search strategy: key word "PCA3"
Records: 218

Clinical trial registries
NIH database
Source: http://clinicaltrials.gov/
Date searched: 8/15/2011
Search strategy: PCA3 [ALL-FIELDS] AND "Completed" [OVERALL-STATUS]
Records: 6

BioMed central
Source: http://www.controlled-trials.com/mrct/
Date searched: 8/15/2011
Search strategy: "PCA3" for completed trials
Records: 0

WHO International Clinical Trials Registry Platform Search Portal
Source: http://apps.who.int/trialsearch/
Date searched: 8/15/2011
Search strategy: Search String = "PCA3" for ALL recruitment status trials
Records: 0

Conference papers and abstracts
American College of Medical Genetics (ACMG)
Source: http://submissions.miracd.com/acmg/
Date searched: 8/15/2011
Search strategy: search string "PCA3 OR Prostate Cancer OR Prostate Cancer Screening"
Records: 2

American Society of Clinical Oncology (ASCO)
Source: http://www.gucasym.org/PastSymposia.aspx
Date searched: 8/15/2011
Search strategy: search string "PCA3"
Records: 6

American Urological Association (AUA)
Source: http://www.auanet.org/content/clinical-practice-guidelines/clinical-practice-guidelines.cfm
Date searched: 8/15/2011

Search strategy: search string “PCA3”
Records: 26

Association of Molecular Pathology (AMP)
Source: http://www.amp.org/meetings/past_meetings.cfm
Date searched: 8/15/2011
Search strategy: not searchable without login
Records: 0

College of American Pathologists (CAP)
Source: http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=reference
Date searched: 8/15/2011
Search strategy: search string “PCA3 OR Prostate Cancer OR Prostate Cancer Screening”
Records: 240

National Comprehensive Cancer Network (NCCN) Annual Congress
Source: http://www.nccn.org/index.asp
Date searched: 8/15/2011
Search strategy: search string “PCA3”
Records: 0

Prostate Cancer Research Initiative (PCRI)
Source: http://www.prostate-cancer.org/pcricms/
Date searched: 8/15/2011
Search strategy: search string “PCA3”
Records: 0

Organizations publishing Guidance or Review Documents
Agence d’évaluation des technologies et des modes d’intervention en santé (AETMIS)
Source: http://www.aetmis.gouv.qc.ca/site/home.phtml
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 0

Australia and New Zealand Horizon Scanning Network (ANZHSN)
Source: http://www.horizonscanning.gov.au/
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 0

Canadian Agency for Drugs and Technologies in Health (CADTH)
Source: http://cadth.ca/
Date searched: 8/15/2011

Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 3 (all excluded; not relevant)

The Cochrane Collaboration (Cochrane)
Source: http://summaries.cochrane.org/
Date searched: 8/15/2011
Search strategy: search string string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR"differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 0

European network for Health Technology Assessment (EUnetHTA)
Source: http://www.eunethta.eu/Public/Search/
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 0

EuroGenTest
Source: http://www.eurogentest.org/
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 0

National Guideline Clearinghouse (NGC)
Source: http://www.guideline.gov/
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
– searches done in different combinations using the above combinations.
Records: 4

National Institute for Clinical Excellence (NICE)
Source: http://www.nice.org.uk/
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").
Records: 1 (excluded; not relevant)

United Kingdom Health Technology Assessment Programme (UK HTA)
Source: http://www.hta.ac.uk/
Date searched: 8/15/2011
Search strategy: search string ("PCA3" OR "prostate cancer antigen 3" OR "DD3" OR "differential display code 3" OR "biomarkers") AND ("prostate cancer" OR "prostatic cancer").

Records: 7

Government documents
RePORTER
Source: http://projectreporter.nih.gov/reporter.cfm
Date searched: 8/15/2011
Search strategy: key word "PCA3"
Records: 26

HSRPROJ
Source: http://wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm
Date searched: 8/15/2011
Search strategy: key word "PCA3"
Records: 0

AHRQ GOLD
Source: http://gold.ahrq.gov/projectsearch/
Date searched: 8/15/2011
Search strategy: key word "PCA3"
Records: 0

Manufacturer database
Source: GenProbe Response to the Request for Scientific Information
Date posted: 12/7/2011
Date searched: Not applicable
Search strategy: Not applicable
Records: 27

References for Review and Abstraction from the Grey Literature Search

PUBMED ID	Authors	Title	Citation
19836788	SJ Eyre, DP Ankerst; JT Wei, et al.	Validation in a multiple urology practice cohort of the Prostate Cancer Prevention Trial calculator for predicting prostate cancer detection.	The Journal of Urology. 2009 Dec; 182 (6) :2653-8

Selected Test Manufacturers for Contact

Manufacturer	Registered® / Trademark Name™	Test Type	Comment
GenProbe	Gen-Probe PROGENSA PCA3	FDA Approval announced 2/17/12	Responded pre-FDA approval
Quest Diagnostics	PCA3 Diagnostic Test	LDT	Did not respond
Bostwick Laboratories	PCA3*Plus*®	LDT	Did not respond
Laboratory Corporation of America	CaPDetect: PCA3	LDT	Did not respond

Contact Information

Gen Probe Incorporated	10210 Genetic Center Drive San Deigo, CA 92121 Phone: 858-410-8000 http://www.genprobe.com
Quest Diagnostics	3 Giralda Farms Madison, NJ 07940 Phone: 800-222-0446 http://www.questdiagnostics.com
Bostwick Laboratories	4355 Innslake Drive Glen Allen, VA 23060 **Phone:** 877-865-3262 http://www.bostwicklaboratories.com
Laboratory Corporation of America	358 South Main Street Burlington, NC 27215 Phone: 336-584-5171 http://www.labcorp.com

Appendix D:
Articles Excluded at Full-Text Level

Articles Excluded at Full Text Level

Reason for Exclusion: Not English-language article

1. J. Rubio-Briones, A. Fernández-Serra, L. Ramírez, L. Rubio, A. Collado, J. Casanova, A. Gómez-Ferrer, J.v. Ricós, J.L. Monrós, R. Dumont, B. Ortiz, I. Iborra, Z. García-Casado, E. Solsona, J.A. López-Guerrero. Actas Urol Esp. 2011 Nov-Dec;35(10):589-96. Epub 2011 Jun 22. Spanish.

Reason for Exclusion: Study participants did not meet study population inclusion criteria **AND** invalid study design

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6. A. Bjartell 2007. PSA and Prostate Cancer Screening: The Challenge of the New Millennium *European Urology*, 52(5): 1284-1286.
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changes as related to the initial prostate specific antigen: data from the prostate, lung, colorectal and ovarian cancer screening trial. *J Urol*, 175: 1286-90; discussion 1290.
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Appendix E: Quality Assessment Criteria and Category Definitions for Nonrandomized Comparative Intervention Studies[84, 85]

- Were the sample definition and selection prospective or retrospective?
- Were inclusion/exclusion criteria clearly described?
- Were participants selected to be representative?
- Was there an attempt to balance groups by design?
- Were baseline prognostic characteristics clearly described and groups shown to be comparable?
- Were interventions clearly specified?
- Were participants in treatment groups recruited within the same time period?
- Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
- Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
- Were outcome measures clearly valid, reliable, and equally applied to treatment groups?
- Were outcome assessors blinded?
- Was the length of followup adequate?
- Was subject attrition below an overall high level (<20 percent)?
- Was the difference in attrition between groups below a high level (<15 percent)?
- Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

The rating of intervention studies encompassed three quality categories:

- **Good** studies meet all criteria; comparable groups were assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments were used and applied equally to the groups; interventions are spelled out clearly; all important outcomes were considered; appropriate attention was given to confounders in analyzing data.
- **Fair** studies had any or all of the following problems, but without the fatal flaws noted in the "poor" category below; comparable groups were assembled initially, but some questions remain about whether some (although not major) differences occurred with followup; measurement instruments were acceptable (although not the best) and were generally applied equally; some, but not all, important outcomes were considered; some, but not all, potential confounders were accounted for.
- **Poor** studies have any of the following fatal flaws; groups assembled initially were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments were used or not applied at all equally among groups (including not masking outcome assessment); key confounders were given little or no attention.

Appendix F:
Quality Assessment of Studies Addressing KQ1 / KQ2 and KQ3

Table F-1. PCA3 testing for the diagnosis and management of prostate cancer – quality of studies addressing KQs 1 and 2

QUADAS Criteria	Adam 2011[1]	Ankerst 2010[2]	Aubin 2010[3]	Cao 2011[4]	de la Taille 2011[5]	Deras 2008[6]	Fradet 2004[7]
Representative study subjects	Yes	Yes	Yes	Uncertain[1]	Yes	Yes	Uncertain
Selection criteria clear	Yes	Yes	Yes	No	Yes	Yes	No
Reference standard correctly identifies PCa	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acceptable period between index test and reference standard	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All or described subset diagnosed by reference standard	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All patients received reference standard, regardless of index result	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reference standard was independent of the index test	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Index test adequately described	Yes	No	Yes	Yes	Yes	Yes	Yes
Reference standard adequately described	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Index test results interpreted without knowledge of reference standard results[2]	Yes	Uncertain	Yes	Uncertain	Yes	Uncertain	Uncertain
Reference standard results interpreted without knowledge of index test[2]	Yes	Uncertain	Uncertain	Uncertain	Uncertain	Yes	Uncertain
Clinical data for interpretation of test results were the same as those expected in practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Uninterpretable/intermediate test results were reported	No	No	No	No	No	No	No
Withdrawals from the study were explained	Yes	None reported	None reported	Yes	Yes Uncertain for fPSA	Yes	Yes
Added criteria:							
Reference standard results interpreted without knowledge of the tPSA test	No	No	No	No	No	No	No
Partial verification bias[3]	Yes	Yes	Yes[4]	Yes	Yes[4]	Yes	Yes
Score	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

The *index test* is PCA3 except for the last three lines, which refer to the tPSA comparator. The *reference standard i*s biopsy.

Table F-1. PCA3 testing for the diagnosis and management of prostate cancer – quality of studies addressing KQs 1 and 2 (continued)

QUADAS Criteria	Hessels 2010[8]	Mearini 2010[9]	Nyberg 2010[10]	Ochai 2011[11]	Ouyang 2009[12]	Perdona 2011[13]	Ploussard 2010[14]
Representative study subjects	Yes	Uncertain[1]	Yes	Yes	Uncertain[1]	Yes	Yes
Selection criteria clear	Yes	Yes	Yes	Yes	No	Yes	Yes
Reference standard correctly identifies PCa	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acceptable period between index test and reference standard	Yes	Yes	Uncertain[1]	Yes	Yes	Yes	Yes
All or described subset diagnosed by reference standard	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All patients received reference standard, regardless of index result	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reference standard was independent of the index test	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Index test adequately described	Yes	No	Yes	Yes	Yes	Yes	Yes
Reference standard adequately described	Yes	No	Uncertain	Yes	No	Yes	Yes
Index test results interpreted without knowledge of reference standard results[2]	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain
Reference standard results interpreted without knowledge of index test[2]	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain
Clinical data for interpretation of test results were the same as those expected in practice	Yes	Uncertain	Yes	Yes	Yes	Yes	Yes
Uninterpretable/intermediate test results were reported	No	Yes	No	No	No	No	No
Withdrawals from the study were explained	Yes	None reported	None reported	Yes	Yes	None reported	Yes
Added criteria:							
Reference standard results interpreted without knowledge of the tPSA test	No	No	No	No	No	No	No
Partial verification bias[3]	Yes	Yes	Yes	Yes	Yes	Yes[4]	Yes[4]
Score	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

The *index test* is PCA3 except for the last three lines, which refer to the tPSA comparator. The *reference standard i*s biopsy.

Table F-1. PCA3 testing for the diagnosis and management of prostate cancer – quality of studies addressing KQs 1 and 2 (continued)

QUADAS Criteria	Rigau 2008[15]	Roobol 2010[16]	Schilling 2011[17]	Tinzl 2004[18]	Wang 2009[19]
Representative study subjects	Yes	Yes	No	Yes	Yes
Selection criteria clear	Yes	Yes	Yes	Yes	Yes
Reference standard correctly identifies PCa	Yes	Yes	Yes	Yes	Yes
Acceptable period between index test and reference standard	Yes	Yes	Uncertain	Yes	Uncertain
All or described subset diagnosed by reference standard	Yes	Yes	Yes	Yes	Yes
All patients received reference standard, regardless of index result	Yes	Yes	Yes	Yes	Yes
Reference standard was independent of the index test	Yes	Yes	Yes	Yes	Yes
Index test adequately described	Yes	Yes	Yes	Yes	Yes
Reference standard adequately described	Yes	Yes	Yes	Uncertain	Yes
Index test results interpreted without knowledge of reference standard results[2]	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain
Reference standard results interpreted without knowledge of index test[2]	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain
Clinical data for interpretation of test results were the same as those expected in practice	Yes	Yes	Yes	Yes	Yes
Uninterpretable/intermediate test results were reported	No	No	No	No	No
Withdrawals from the study were explained	Yes	Yes	Yes	Yes	Yes
Added criteria:					
Reference standard results interpreted without knowledge of the tPSA test	No	No	No	No	No
Partial verification bias[3]	Yes	Yes	Yes	Yes	Yes
Score	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

The *index test* is PCA3 except for the last three lines, which refer to the tPSA comparator. The *reference standard i*s biopsy.

[1]'Uncertain' indicates that information was not provided to determine the answer to the question; it does not mean that the answer to the question is 'No'.

[2] Information on blinding is often not reported, so the category of Uncertain does not mean that blinding did not occur.

[3] Partial verification bias because men with elevated tPSA and/or positive digital rectal exam who did not accept biopsy are considered missing.

[4] There is an additional partial verification bias in this study due to a limitation on the range of tPSA values that are included (i.e., the so called 'grey zone' results in the range of 2.5 to 10.0 ng/mL).

Table F-2. PCA3 testing for the diagnosis and management of prostate cancer – quality of studies addressing KQ3

QUADAS Criteria	Auprich 2011[20]	Cao 2011[4]	de la Taille 2011[5]	Hessels 2010[8]	Kasuda 2011[21]	Liss 2011[22]
Representative study subjects	Yes	Uncertain	Yes	Yes	Uncertain[1]	Yes
Selection criteria clear	Yes	Yes	Yes	Yes	Yes	Yes
Reference standard correctly identifies PCa or other outcome	Yes	Yes	Yes	Yes	Uncertain	Yes
Acceptable period between index test and reference standard	Yes	Yes	Yes	Yes	Yes	Yes
All or described subset diagnosed by reference standard	Yes	Yes	Yes	Yes	Yes	Yes
All patients received reference standard, regardless of index result	Yes	Yes	Yes	Yes	Yes	Yes
Reference standard was independent of the index test	Yes	Yes	Yes	Yes	Yes	Yes
Index test adequately described	Yes	Yes	Yes	Yes	Uncertain	Yes
Reference standard adequately described	Yes	Yes	Yes	Yes	No	Yes
Index test results interpreted without knowledge of reference standard results[2]	Uncertain	Uncertain	Yes	Uncertain	Uncertain	Uncertain
Reference standard results interpreted without knowledge of index test[2]	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain
Clinical data for interpretation of test results were the same as those expected in practice	Yes	Yes	Yes	Yes	Yes	Yes
Uninterpretable/intermediate test results were reported	No	No	No	No	Yes	No
Withdrawals from the study were explained	Yes	Yes	Yes Uncertain for fPSA	Yes	Uncertain	Yes
Added criterion: *Clinical followup*	No	No	No	No	Yes	No
Score	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

Table F-2. PCA3 testing for the diagnosis and management of prostate cancer – quality of studies addressing KQ3 (continued)

QUADAS Criteria	Nakanishi 2008[23]	Ploussard 2010[14]	Tosian 2010[24]	Vlaeminck-Guillem 2011[25]	Whitman 2008[26]
Representative study subjects	Yes	Yes	Yes	Yes	Yes
Selection criteria clear	Yes	Yes	Yes	Yes	Yes
Reference standard correctly identifies PCa or other outcome	Yes	Yes	Uncertain	Yes	Yes
Acceptable period between index test and reference standard	Yes	Yes	Yes	Yes	Yes
All or described subset diagnosed by reference standard	Yes	Yes	Yes	Yes	Yes
All patients received reference standard, regardless of index result	Yes	Yes	Yes	Yes	Yes
Reference standard was independent of the index test	Yes	Yes	Yes	Yes	Yes
Index test adequately described	Yes	Yes	Yes	Yes	Yes
Reference standard adequately described	Yes	Yes	No	Yes	Yes
Index test results interpreted without knowledge of reference standard results[2]	Uncertain	Uncertain	Uncertain	Uncertain	Uncertain
Reference standard results interpreted without knowledge of index test[2]	Uncertain	Uncertain	Uncertain	Yes	Uncertain
Clinical data for interpretation of test results were the same as those expected in practice	Yes	Yes	Uncertain	Yes	Yes
Uninterpretable/intermediate test results were reported	No	No	Yes	No	No
Withdrawals from the study were explained	None reported	None reported	No	Uncertain	None reported
Added criterion: *Clinical followup*	No	No	Yes	No	No
Score	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

[1] 'Uncertain' indicates that information was not provided to determine the answer to the question; it does not mean that the answer to the question is 'No'.
[2] Information on blinding is often not reported, so the category of 'Uncertain' does not mean that blinding did not occur.

Appendix G:
DistillerSR Abstract and Title Screening Form

Is the article in English, or was an English translation available from the journal?

- Yes
- No
- Uncertain

Were the study participants men in any of these specific populations:

- men at risk for prostate cancer based on elevated PSA (lowest cutoff > 2.5 ng/mL) and/or positive DRE?
- men at risk for prostate cancer based on elevated PSA and/or positive DRE, and one or more negative prostate biopsies?
- men with a positive prostate biopsy?

- Yes
- No
- Uncertain

Does at least one of the study descriptions below apply?

- A matched study or systematic review/meta-analysis of PCA3 and one or more designated comparators(s) (tPSA, fPSA, cPSA, PSA velocity, validated nomograms) used to inform a decision about initial or repeat prostate biopsy.
- A matched study or systematic review/meta-analysis of PCA3 and comparators (Gleason score, tumor stage/volume) used to assess prognosis/tumor aggressiveness.
- A matched study or systematic review/meta-analysis of PCA3 alone or in combination with comparators (tPSA, PSA velocity) as part of triage for active surveillance or aggressive treatment.
- A systematic review and/or meta-analysis of matched studies of PSA and one or more comparator(s) used to inform decisions about initial or repeat prostate biopsy.
- A systematic review, meta-analysis or matched study of any two or more comparators other than PSA used to inform decisions about initial or repeat prostate biopsy.

Note: Acceptable study designs included randomized or non-randomized controlled trials, prospective or retrospective cohort studies, diagnostic accuracy and case-control studies.

- Yes
- No
- Uncertain

Is this an unmatched diagnostic accuracy study (or systematic review/meta-analysis of such studies) on PCA3 or other comparators?

Select an Answer *[If Yes, paper was filed for future reference but ineligible for abstraction.]*

Appendix H:
DistillerSR Full-Text Article Screening Form

Question Text	Type	Question Header	Answer Text	Answer Headers
Was there an English language article or a translation available from the journal?	Radio	English language	Yes, No, Uncertain	Yes, No, Uncertain
Were the study participants men in any of these specific populations: • men at risk for prostate cancer based on elevated PSA (lowest cutoff > 2.5 ng/mL) and/or positive DRE? • men at risk for prostate cancer based on elevated PSA and/or positive DRE, and one or more negative biopsies? • men with a positive prostate biopsy?	Radio	Appropriate study participants	Yes, No, Uncertain	Yes, No, Uncertain
Does at least one of the study descriptions below apply? • A matched study or systematic review/meta-analysis of PCA3 and one or more designated comparators(s) (tPSA, fPSA, cPSA, PSA velocity, validated nomograms) used to inform a decision about initial or repeat prostate biopsy. • A matched study or systematic review/meta-analysis of PCA3 and comparators (Gleason score, tumor stage/volume) used to assess prognosis/tumor aggressiveness. • A matched study or systematic review/meta-analysis of PCA3 alone or in combination with comparators (tPSA, PSA velocity) as part of triage for active surveillance or aggressive treatment. • A systematic review and/or meta-analysis of matched studies of PSA and one or more comparator(s) used to inform decisions about initial or repeat prostate biopsy. • A systematic review, meta-analysis or matched study of any two or more comparators other than PSA used to inform decisions about initial or repeat prostate biopsy. • A systematic review, meta-analysis or comparative study evaluating long-term outcomes. Note: Acceptable study designs included randomized or non-randomized controlled trials, prospective or retrospective cohort studies, diagnostic accuracy and case-control studies.	Radio	Appropriate study description	Yes, No, Uncertain	Yes, No, Uncertain
Did study participants undergo prostate biopsy or prostatectomy as part of a diagnostic workup for prostate cancer?	Radio	Biopsy or RP	Yes, No, Uncertain	Yes, No, Uncertain
Did the biopsy include a minimum of 6 cores?	Radio	≥ 6 biopsy cores	Yes, No	Yes, No

			Uncertain	Uncertain
Did the study report provide one or more of the criteria used to characterize tumors (e.g., Gleason score, tumor burden, staging)? *[Required only for KQ3]*	Radio	Tumor characteristics	Yes, No, Not Applicable, Uncertain	Yes, No, Not Applicable, Uncertain
For patients who were candidates for initial or repeat biopsy, did the study provide: • estimate(s) of diagnostic accuracy for prostate cancer; • short-term outcomes (e.g., decision to biopsy or not, medical and psychological complications of biopsy); and/or • long-term outcomes (e.g., mortality, morbidity, quality of life, harms) based on intervention. OR For patients who were biopsy positive and being triaged for active surveillance or aggressive treatment, did the study provide: • estimates of diagnostic accuracy for aggressive disease; • short-term outcomes (e.g., decisions regarding aggressive surveillance or treatment); and/or • long-term outcomes (e.g., mortality, morbidity, quality of life, harms) based on intervention.	Radio	Outcomes reported	Yes, No, Uncertain	Yes, No, Uncertain

Appendix I: DistillerSR Data Extraction Forms

Study Description

Question Text	Answers Text
First Author (Last, First Initial):	
Year of Publication:	
Study design:	RCT, Non-randomized controlled trial, Non-randomized comparative study, Systematic review/MA, Diagnostic accuracy study, Case-control study
Is this a matched study?	Yes, No
Does this study report systematic review data within it?	Yes, No
Which key question(s) does this article address? KQ1:In patients with elevated PSA and/or an abnormal DRE who are candidates for initial prostate biopsy, what is the comparative effectiveness of PCA3 testing as a replacement for, or supplement to, standard tests (e.g., elevated total PSA values, decreased percent-free PSA levels, elevated PSA velocities, complexed PSA, or externally validated nomograms) with regard to diagnostic accuracy, intermediate outcomes and/or long-term health outcomes? KQ2: In patients with elevated PSA and/or an abnormal DRE who are candidates for repeat prostate biopsy, what is the comparative effectiveness of PCA3 testing as a replacement for, or supplement to, standard screening tests (e.g., elevated total PSA values, decreased percent free PSA levels, elevated PSA velocities, complexed PSA, or externally validated nomograms) with regard to diagnostic accuracy, intermediate outcomes and/or long-term health outcomes? KQ3: In patients with a positive biopsy for prostate cancer who are being evaluated to distinguish between indolent and aggressive disease, what is the effectiveness of using PCA3 testing alone, or in combination with the standard prognostic workup (e.g., tumor volume, Gleason score, clinical staging) or monitoring tests (e.g., PSA, PSA velocity) with regard to diagnostic accuracy, intermediate outcomes and/or long-term health outcomes?	KQ1, KQ2, KQ3, All, None
Does this article report data on men who are first time biopsies, repeat biopsies, mixed or uncertain?	First biopsies, Repeat biopsies, Mixed, Uncertain, Not applicable
Title:	
Is there more than one study site?	Yes, No
Total number of study sites	
List the name of each study site below:	Institution 1-7
Name of Study Site:	
Start Date and End Date (mm/dd/yy):	
Number at enrollment:	
Setting(s):	Hospital/clinic, Referrral center, Screening FU, Other
Follow-up assessed?	Yes, No
Follow-up Number:	

Follow-up Percent (%):	
BOTH not provided?	Yes
Follow-up losses explained?	Yes, No-Not Provided
Follow-up (months):	Mean, SD, Median, Range, IQR
Source(s) of Funding:	Not Provided, Not Externally Funded, Departmental, Industry, Government, Private Funding, Other
Author-industry relationship disclosures:	None, Yes – describe, Not provided
Does this article reference other publications where this dataset, subsets of this dataset, or this study population were used?	Yes – Indicate reference, No
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	
FACT-CHECKING FOR THIS ARTICLE HAS BEEN COMPLETED BY:	
Final fact-checking completed on (mm/dd/yy):	
THIS ARTICLE IS NOT A PCA3 ARTICLE?	Yes, No

Participant Characteristics & Inclusion Criteria

Question Text	Answers Text
Age:	Mean, SD, Median, Range, IQR
Men on meds excluded:	Yes, No, Not specified
Race: African-Americans N(%):	
Caucasian N(%):	
Hispanic N(%):	
Asian N(%):	
Other N(%):	
Are there men with benign prostatic hyperplasia (BPH)?: Are there men with high-grade prostate intraepithelial neoplasia (HGPIN)?: Are there men with atypical small acinar proliferation (ASAP)?: Are there men with prostatitis?:	Yes –N, %, No-Excluded, Unknown
Were results of DRE reported outside of inclusion?	Yes, No
Number of men who had DRE Test:	
Number and % DRE positive:	
Number and % DRE negative:	
PSA testing in group?	Yes, No
tPSA cutoff 1-4: Number tested, Number positive, % positive	
Were men included based on their DRE test?	Yes-Number, No, Unknown
Number and % DRE positive	
One or more previous negative biopsies:	Yes-N, %, No

Positive Family History:	Yes-N, %, No, Unknown
African-American:	Yes-N, %, No, Unknown
Age Cutoff:	Yes-Specify, N, %, No, Unknown
Scheduled for biopsy – specific reason for biopsy unknown:	Yes-N, %, No, Unknown
ABSTRACTOR COMMENTS If you would like to leave a comment pertaining to the information above indicate your name below:	

Specimen/Assay Description

Question Text	Answers Text
Collection by attentive prostate massage:	Yes, No, Not provided
Specimen:	Urine – sedimented, Urine – unsedimented, Prostatic ejaculate
Name of transport media:	
Transport time (hours):	
Holding temperature (Celsius):	
Storage temperature (-C):	
Method used:	Quantitative Real Time PCR, Nucleic acid sequence based amplification, Transcription-mediated Amplication
Assay used identified as:	1st, 2nd or 3rd generation test
	uPM3, PCA3Plus, Progensa, Aptima, “Gen-Probe test”, Test not specified
Housekeeping gene:	PSA mRNA, Other, Not provided
Result unit:	PCA3 Score, Other
Testing blinded to outcomes:	Yes, No, Not provided
Number and percent of samples with insufficient mRNA:	
Number and percent of reportable results:	
PCA3 losses explained?	Yes, No
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

PCA3 by Cutoff

Question Text	Answer Text
This page does not pertain to this study?	Yes (move to next form), No (complete #2)
This study has more than one PCA3 cutoff?	Yes (complete #3 and #4), No (skip #3)
Indicate PCA3 cutoff number:	PCA2 cutoff 1-6
For each, PCA3 cutoff value:	

Negative biopsy summary for PCA3::	Mean, SD, Median, Range, IQR
Negative biopsy summary for PCA3:	Mean, SD, Median, Range, IQR
Number Tested:	
Raw data:	TP = Test positive, biopsy positive, FP = Test positive, biopsy negative, FN = Test negative, biopsy positive, TN = Test negative, biopsy negative
Performance data	Sensitivity, CI, p-value; Specificity, CI, p-value; Positive predictive value, CI, p-value, Negative predictive value, CI, p-value, Odds ratio, Likelihood ratio
Was a univariate analysis conducted for Diagnostic Odds Ratio (DOR)?	Yes-Predictive Accuracy, p-value, No
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Total PSA by Cutoff (Identical format used for total PSA, free PSA, PSA density, PSA doubling time, PSA velocity, complexed PSA, externally validated nomograms)

Question Text	Answer Text
This page does not pertain to this study?	Yes (move to next form), No (complete #2)
This study has more than one tPSA Cutoff?	Yes (complete #3 and #4), No (skip #3)
Indicate tPSA Cutoff number:	tPSA Cutoff 1-6
For each: tPSA Cutoff Value:	
Negative biopsy summary for PSA::	Mean, SD, Median, Range, IQR
Negative biopsy summary for PSA:	Mean, SD, Median, Range, IQR
Number Tested:	
Raw data:	TP = Test positive, biopsy positive, FP = Test positive, biopsy negative, FN = Test negative, biopsy positive, TN = Test negative, biopsy negative
Performance data	Sensitivity, CI, p-value; Specificity, CI, p-value; Positive predictive value, CI, p-value, Negative predictive value, CI, p-value, Odds ratio, Likelihood ratio
If compared to PCA3 identify method for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
Was a univariate analysis conducted for Diagnostic Odds Ratio (DOR)?	Yes-Predictive Accuracy, p-value, No
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Prostate biopsy and prostatectomy

Question Text	Answer Text
Indicate for which the total number is given:	Biopsies, Prostatectomies, Both
Indicate total N reportable biopsies:	
Indicate total N prostatectomies:	
Biopsy losses explained?	Yes, No, Unknown
Number of cores per biopsy:	
Cores per biopsy:	Mean, SD, Median, Range, IQR
Interpretation blinded to study categories:	Yes, No, Not provided
Positive biopsies:	N, %
Percent cores with cancer:	% or Not Provided
Cores with cancer > 33%:	Number, %
% cancer per core:	Mean %, SD, Median, Range, IQR
Gleason score: 6; 7; >6; >7; ≥ 7:	N, %
Gleason Score cutoff not listed above:	Yes, No
Other Gleason score cutoffs: 1-3	Name cutoff, N, %
PSA Density	Mean, SD, Median, Range, IQR
Biopsy Pathological stages: T1c; T2a; T2b; T2c; T3	N, %
Other biopsy pathological stage:	Name stage, N, %
Prostate Volume (cc):	Mean, SD, Median, Range, IQR
Are there “Insignificant findings” based on Epstein criteria (clinical stage T1c, PSA density <0.15, Gleason score <6, presence of PCa in fewer than 3 cores, <33% of cores are positive):	Meets Epstein Criteria- N, %; Does NOT Meet Epstein Criteria
Radical prostatectomy staging: pT0; pT1, pT2; pT3	N, %
Extracapsular extension:	N, %
Perineural invasion:	N, %
Nodal involvement:	N, %
Seminal vesicle invasion:	N, %
Abnormal MRI:	N, %
Abnormal TRUS:	N, %
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Gleason Score

Question Text	Answer Text
This page does not pertain to this study?	Yes (move to next form), No (complete #2)
This study has more than one Gleason score Cutoff?	Yes (complete #3 and #4), No (skip #3)
Indicate Gleason Score Cutoff number:	Cutoff 1-6
Indicate Gleason Score Cutoff Value:	

Number of men WITH this biopsy result who are having a PCA3 test:	
PCA3 value Mean:	
If compared to PCA3, identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
PCA3 value Standard Deviation (SD):	
PCA3 value Median:	
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
PCA3 value Range:	
PCA3 value IQR:	
Area Under the Curve (AUC):	Value, CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Was a univariate analysis conducted for Diagnostic Odds Ratio (DOR)?	Yes-Predictive Accuracy, p-value, No
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Pathological Staging

Question Text	Answer Text
This page does not pertain to this study?	Yes (move to next form), No (complete #2)
This study presents information on more than one pathological staging result:	Yes (complete #3 and #4 and skip to Table 1.), No (skip #3 and complete #4)
Identify path result number:	1-6
Identify pathological staging result:	T1c, T2, T2a, T2b, T2c, Other
Number of men WITH this biopsy result who are having a PCA3 test:	
PCA3 value Mean:	
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
PCA3 value Standard Deviation (SD):	
PCA3 value Median:	
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other

p-value:	
PCA3 value Range:	
PCA3 value IQR:	
Area Under the Curve (AUC):	Value, CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Epstein Criteria

Question Text	Answer Text
This page does not pertain to this study?	Yes (move to next form), No (complete #2)
Does this study more than one set of criteria?	Yes (complete #3 and #4), No (skip #3)
Describe components of Epstein criteria 1-5	
Indicate Epstein Criteria category (category defined by each set of criteria):	Indolent, Significant, Other
Is the Epstein criteria modified?	Yes, No
Criteria Set 1-5:	Describe criteria
Number of men WITH this biopsy result having a PCA3 test:	
PCA3 value Mean:	
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
PCA value Standard Deviation (SD):	
PCA3 value Median:	
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
PCA3 value Range:	
PCA3 value IQR:	
Area Under the Curve (AUC):	Value, CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
p-value:	
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

AUC

Question Text	Answer Text
Test 1:	PCA3
Units:	
Reference standard:	Prostate biopsy, Prostatectomy
AUC Group 1:	Name
G 1. Area Under the Curve (AUC):	Value, 95% CI, p-value
Was AUC reported for more than one group?	Yes, No
AUC Group 2:	Name
G 2. Area Under the Curve (AUC):	Value, 95% CI, p-value
AUC Group 3:	Name
G 3. Area Under the Curve (AUC):	Value, 95% CI, p-value
AUC Group 4:	Name
G 4. Area Under the Curve (AUC):	Value, 95% CI, p-value
AUC Group 5:	Name
G 5. Area Under the Curve (AUC):	Value, 95% CI, p-value
Test 2-6	Names 2-6
Units:	
Reference standard:	Prostate biopsy, Prostatectomy
AUC Group 1:	Name
G 1. Area Under the Curve (AUC):	Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Was AUC reported for more than one group?	Yes, No
AUC Group 2:	Name
G 2. Area Under the Curve (AUC):	Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
AUC Group 3:	Name
G 3. Area Under the Curve (AUC):	Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
AUC Group 4:	Name
G 4. Area Under the Curve (AUC):	Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
AUC Group 5:	Name

G 5. Area Under the Curve (AUC):	Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Nomogram 1-3:	Name
Variables used in nomogram (must be 3 or more):	Age, family history, race, DRE result, previous negative biopsy, PCA3, tPSA, fPSA, cPSA, PSA velocity, Gleason score, other
Method for score calculation:	
Reference Standard:	Prostate biopsy, Prostatectomy
Nomogram AUC Group 1:	Name, Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Was AUC reported for more than one group?	Yes, No
Nomogram AUC Group 2	Name, Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Nomogram AUC Group 3:	Name, Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Nomogram AUC Group 4:	Name, Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
Nomogram AUC Group 5:	Name, Value, 95% CI, p-value
If compared to PCA3 identify test for comparison:	McNemar, Fisher's exact, paired t-test, Chi-square, Wilcoxon rank sum, Kruskal-Wallis, Pearson correlation, non-parametric comparison of AUC (DeLong), Other
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	
ENTER YOUR COMMENTS:	

Matched Analysis Data
Matched Study Data – Multivariate Analysis

Question Text	Answer Text
Is this study a matched analysis?	Yes (complete Section 1), No (skip to Section 2)
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Section 1. Matched Analysis Data

Positive Biopsy:

	Comparator Positive	Comparator Negative
PCA3 Positive		
PCA3 Negative		

Negative Biopsy:

	Comparator Positive	Comparator Negative
PCA3 Positive		
PCA3 Negative		

Identify Comparator:

Section 2. Multivariate Logistical Regression Analysis

	Base ModelOdds Ratio (OR)	Base Model(95% CI)	Base Model (p-value)	Base Model + Group 1 (OR)	Base Model + Group 1 (95% CI)	Base Model + Group 1 (p-value)	Base Model + Group 2 (OR)	Base Model + Group 2 (95% CI)	Base Model + Group 2 (p-value)	Base Model + Group 3 (OR)	Base Model + Group 3 (95% CI)	Base Model + Group 3 (p-value)	Base Model + Group 4 (OR)	Base Model + Group 4 (95% CI)	Base Model + Group 4 (p-value)
Variable 1:															
Variable 2:															

Variable 3:															
Variable 4:															
Variable 5:															
Variable 6:															
Variable 7:															
Variable 8:															
Variable 9:															
Variable 10:															
Predictive Accuracy:															
Result OTHER:															

Identify Group 1 in the Model:

Identify Group 2 in the Model:

Identify Group 3 in the Model:

Identify Group 4 in the Model:

Quality - QUADAS

Question Text	Answers Text
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes, No, Uncertain
Were selection criteria clearly described?	Yes, No, Uncertain
Is the reference standard likely to classify the target condition correctly?	Yes, No, Uncertain
Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes, No, Uncertain
Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	Yes, No, Uncertain
Did patients receive the same reference standard regardless of the index test result?	Yes, No, Uncertain
Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard?)	Yes, No, Uncertain
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes, No, Uncertain
Was the execution of the reference standard described in sufficient detail to permit replication of the refererence standard?	Yes, No, Uncertain
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes, No, Uncertain
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes, No, Uncertain
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes, No, Uncertain
Were uninterpretable/intermediate tests results reported?	Yes, No, Uncertain
Were withdrawals from the study explained?	Yes, No, Uncertain
Overall Quality Assessment: (To be completed by Dr. Gutman or Dr. Bradley ONLY)	
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:	

Appendix J: Detailed Description of PCA3 and Total PSA Interpretive Analysis

Introduction to Partial Verification Bias for Total PSA (tPSA) Elevations

Study design is an important inclusion criterion for this comparative review, because tPSA measurements, the main comparator to PCA3, are integral to men's decision-making regarding prostate biopsy. Men will be offered prostate biopsy based on the extent of tPSA elevations, suspicious findings on a digital rectal exam (DRE), a combination of the two or, less commonly, other risk factors such as family history or race. In order to obtain an unbiased estimate of diagnostic accuracy for tPSA at specific cut-offs, it is necessary that the identification of prostate cancer not be related to tPSA levels. This is a potential problem as most clinicians believe that higher tPSA levels are indicative of a higher likelihood for the presence of prostate cancer. Men are more likely to undergo prostate biopsy, if the tPSA is high (*e.g.*, 10-20 ng/mL), rather than close to lower cut-offs used to define a positive tPSA screening test *(e.g.*, 3-4 ng/mL). If a study reports results in which biopsy is tPSA-related, the sensitivity and specificity at select tPSA cut-offs will not be accurate. If those not accepting biopsy are considered missing this type of bias has been termed 'partial verification' bias.

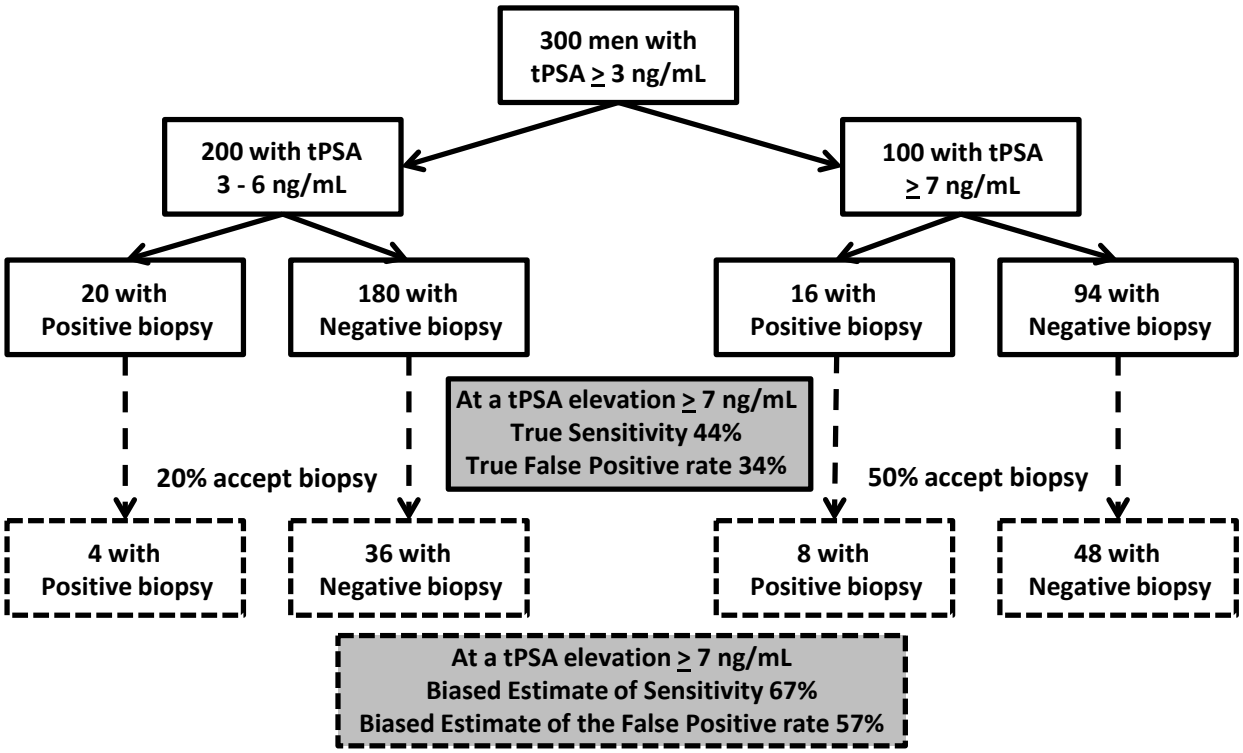


Figure J1. A schematic showing the impact of partial verification bias on the sensitivity and false positive rate for total PSA (tPSA) and prostate biopsy. A complete description is provided in the text.

An example of how partial verification bias occurs is shown in Figure J1. These numbers are intended to be representative of clinical practice, but are mainly designed to demonstrate partial

verification bias in diagnostic studies of tPSA and prostate cancer. A subset of 300 men have been selected from a cohort of as many as 3,000 men over 50 years of age based on having tPSA values of 3 ng/mL or higher. The remaining 2,700 men had low tPSA values and are not shown. For simplicity, consider all men with tPSA over three to be categorized into only two groups defined by the extent of tPSA elevation (3-6 ng/mL and ≥7 ng/mL). The prevalence of prostate cancer will be somewhat lower (10%) in the group with lower tPSA than the prevalence (16%) in the group with higher tPSA. At this point, the 'true' sensitivity and associated false positive using the cut-off of 7 ng/mL can be determined to be 44% (16/(16+20)) and 34% (94/(94+180)), respectively (shaded box with solid outline). The resulting likelihood ratio is 1.29 (44/34). These correct results would have been obtained, if all 300 men were to have had biopsies. An unbiased result could also be obtained, if a subset had biopsies and the remaining men were followed longitudinally to identify future cancer diagnoses.

In clinical practice, however, the uptake rate for prostate biopsy will depend on the group to which the men belong. In the group with lower tPSA levels, the uptake rate may be 20%. In the group with higher tPSA levels, the uptake rate may be 50%. These uptake rates, and results in men choosing biopsy are shown by the dashed arrows and boxes. Among the group of men choosing biopsy based loosely on the tPSA level, the sensitivity and false positive rate are now 67% (8/(8+4)) and 57% (48/(48+36)), respectively. The corresponding likelihood ratio is 1.18 (67/57).

Figure J1 shows that partial verification bias in this setting tends to overestimate the sensitivity (67% versus 44%), as the men with cancer having with low tPSA are less likely to be identified (false negatives). The bias will also overestimate the false positive rate (57% versus 34%) as the men without cancer having low tPSA are also less likely to be identified (true negatives).

The Literature Regarding Partial Verification Bias for total PSA elevations

An important paper on partial verification bias and diagnostic accuracy of tPSA was in a population-based screening test.[1] That is, the study focused on a data set of men having tPSA testing and those with both normal and elevated tPSA levels may have had biopsies. This differs from the setting of the current review which focuses on using the extent of tPSA elevations among men already identified as being 'high risk' due to at least modest elevations of tPSA (e.g., >2.5 ng/mL, ≥3 ng/mL) and/or other factors already described. Punglia and colleagues reported that partial verification bias has two separate and important effects: 1) the performance of tPSA measurements is actually better than the reported performance subject to partial verification bias, and 2) the cut-off level at which select sensitivities and associated false positive rates occur are quite different in biased versus unbiased studies. For example, they reported the area under the ROC curve for men under age 60 years to be 0.69 with partial verification bias, and 0.86 after accounting for the bias ($p<0.001$). In that same group, a cut-off of 4.1 ng/mL was associated with a sensitivity and false positive rate of about 43% and 22% with bias; 18% and 2% after adjustment. One limitation to that study was the use of a categorical uptake rate to model the presence of cancer in men without biopsies. This may have caused at least some of the difference in performance. A later study also adjusted for verification and found that the ROC curve was essentially unchanged (AUC 0.682 among verified, and 0.678 after accounting for partial verification).[2] However, a relatively high proportion (64%) of the population was

biopsied. We verified by in-house modeling that in the setting of this review, it is likely that the ROC will not be substantially impacted (uptake proportional to tPSA, ranging from 5% to 50%, with 30% overall verification). Several studies have assumed that a single cut-off will be used, and focus only on correcting the estimates of sensitivity and specificity at that cut-off, and do not consider the issue of whether the biased estimate falls on the true ROC curve or not.[3-7]

There are two important factors that appear to influence the extent of partial verification bias:

1. the differential rates of cancer (positive prostate biopsy) in the group below the tPSA cut-off compared to the group above the cut-off. If the rates of cancer are the same in the two groups, no partial verification bias will occur. The greater the relative difference (rate ratio) between groups, the larger effect the partial verification bias will have.
2. the differential biopsy uptake rates in the two groups. If the biopsy uptake rates are the same, there will be no partial verification bias, even if the rates of cancer are different. Analogously, if there is no difference in the cancer rates, there will be no partial verification bias even if the uptake rates differ.

The setting of the current evidence review differs from that explored by Puglia and colleagues in two important ways. First, the differential rate of cancer in studies relevant to this review (all having at least modest elevations) is likely to be considerable less. This suggests that the partial verification bias would have less impact in the current setting. Second, the biopsy uptake rate in our two groups is likely to be more similar. Lastly, the overall uptake rate will also be higher, as all of the men in our setting would all have an elevated tPSA (and/or positive DRE or other factor). All of these differences would tend to reduce the effect of partial verification bias. Of most importance is the finding that the ROC curves (and, by extension, AUC and sensitivity/specificity estimates) are not affected by partial verification bias for tPSA measurements.

Review of methodology specific to the PCA3 / tPSA comparison

The aims of the following interpretative analyses are to estimate the unbiased performance of tPSA and PCA3 to identify men with a negative, or positive, biopsy The analysis will be anchored by two important findings. First, the ROC curves for tPSA (and for PCA3) are not influenced by the partial verification bias. Thus, any set of parameters we might generate, would have to fit that data. Second, the literature contains sufficient data to estimate the needed parameters, but those estimates will be subject to the partial verification bias for tPSA (not for PCA3). If the reported tPSA parameters can be 'unbiased' and fitted to the relevant ROC curve, then a comparison between tPSA and PCA3 at selected cut-off levels can be made. Based on published data, the distributions of these markers are likely to be Gaussian, after a logarithmic transformation. To simplify the analysis, we have also chosen to force the logarithmic standard deviations to be the same. According to the literature, this is a reasonable assumption. The secondary aims of these analyses are to provide improved templates for more reliably exploring the comparison of prostate cancer markers and assist in providing methods to more fully inform decision-making by men and their health care providers.

Interpretative analysis for PCA3

Figure J2 shows how overlapping distributions of PCA3 can be used to generate sensitivity and false positive rates (1-specificity). The baseline data used to estimate the median and logarithmic SDs are provided in the body of the evidence review (Table 11). Only a small subset of studies reported sufficient data for this analysis and as such, provide somewhat limited information about the true distribution parameters. Although the reported median values are variable, the PCA3 scores are about twice as high in those with a positive versus a negative biopsy. These results are not subject to partial verification bias because tPSA and PCA3 levels are independent (body of the evidence review, Table 20). There is more consensus on the logarithmic SDs being about 0.40. Median PCA3 scores of 20 and 45 for the two groups, result in a good fit to the consensus ROC data shown in the next paragraph.

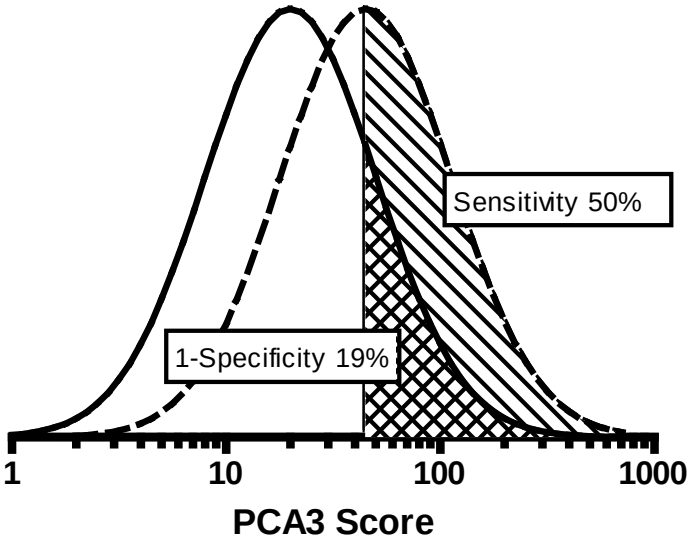


Figure J2. Overlapping distributions of PCA3 scores in men with negative or positive biopsies.
The overlapping distributions are described by log Gaussian parameters (1.301, 0.40: solid line, negative and 1.653, 0.40; dashed line, positive). A vertical line has been drawn at 45 to demonstrate how these data can be used to generate sensitivity (50%, hatched area) and the false positive rate (19%, cross-hatched area). Moving the line left and right will generate an ROC curve.

Figure J3 shows seven points on the ROC curve for PCA3 derived from the literature review. These points correspond to false positive rates of 20% through 80%, in 10% intervals. The dashed line indicates a 'useless' test as a reference (sensitivity is equal to the false positive rate). The solid line has been derived from the overlapping distributions show in Figure J2, and fit reasonably well. It is not possible to formally test the fit, as most of the original data were obtained from the published figures rather than from original data. This model allows the interpolation of sensitivity and false positive rates across the range of values, and provides an estimate of what PCA3 score is associated with that test performance. According to the few relevant studies, PCA3 scores in men with negative biopsies vary between reports, so the absolute PCA3 cut-off may not be appropriate in every setting. For this reason, the results of this analysis should be used only as a guide. This gap in knowledge could be addressed in future research by examining normalizing functions such as multiple of the median PCA3 score, where the median level is determined in a healthy male population without prostate cancer.

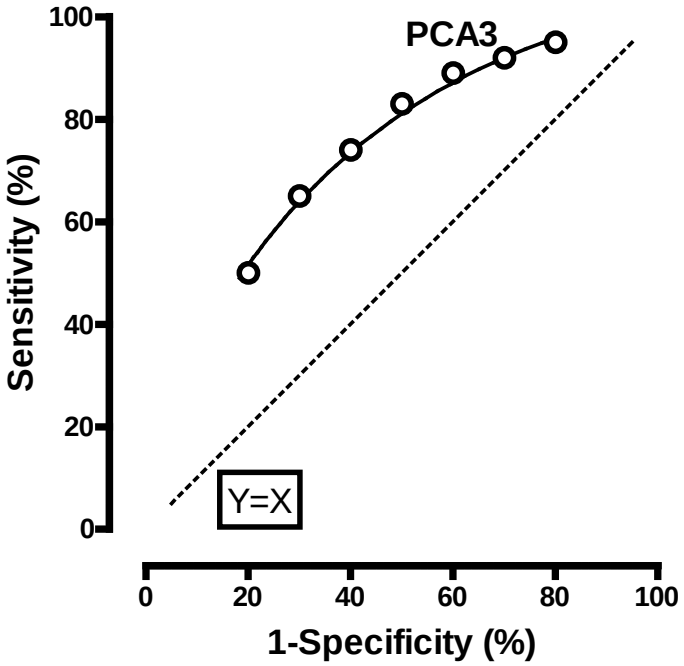


Figure J3. A fitted ROC curve for PCA3 scores.
The figure shows that the overlapping distributions provided in Figure J2 Adequately fit the observed ROC data from the literature (open circles). A simple cumulative Gaussian model can now be used to generate sensitivity at false positive rates between 20% and 80%.

Interpretative analysis for tPSA

Similar data were available for tPSA, but with the caveat that partial verification bias must be accounted for in selection of parameters. The literature was more consistent in the reported median and logarithmic SDs for tPSA (body of the text, Table 9). In general, the medians were 6 ng/mL and 9 ng/mL, in those with negative and positive biopsies, respectively. The consensus logarithmic SD was about 0.31. Unfortunately, partial verification bias will inflate the median value, as lower tPSA measurements in men both with and without cancer will be under-represented. The bias will also tend to shrink the logarithmic standard deviation. In order to estimate how much lower and broader to make the distributions, we generated log Gaussian distributions and subjected them to partial verification bias to study the effect. In one of these models, the uptake rate was estimated to be the tPSA value divided by 20, with an upper limit of 0.5 (50% uptake). For example, men with a tPSA of 8 would have an uptake rate of 40% (8/20) while those with a tPSA of 4 would have a 20% uptake rate. We found the variance increased by about 30% to 40%, while the median value was reduced by 35% to 45%. Applying these correction factors to the reported medians and logarithmic SD, and then further requiring the distributions to fit the reported tPSA ROC curve, results in the data shown in Figure J5. These data must be viewed as approximate. However, knowing that the necessary data to produce an observed and unbiased estimate is likely to be unattainable, it may be preferable to reporting that the analysis cannot proceed due to the existence of partial verification bias.

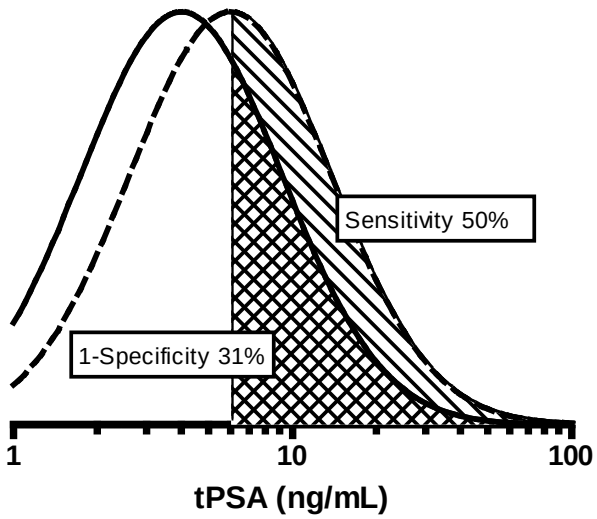


Figure J4. Overlapping distributions of tPSA measurements in men with negative or positive biopsies, after accounting for partial verification bias.
The overlapping distributions are described by log Gaussian distributions (0.602, 0.36: solid line, negative biopsy and 0.778, 0.36; dashed line, positive biopsy). A cut-off (vertical line) has been drawn at 6 ng/mL to demonstrate how these data can be used to generate sensitivity (50%, hatched area) and the false positive rate (31%, cross-hatched area). Moving the line left and right will generate the data for an ROC curve.

Figure J5 shows seven points on the ROC curve for tPSA derived from the literature review. Only data from the six studies that did not restrict tPSA measurements to the 'grey zone' were included (body of the text, Table 11). These points will be essentially unchanged whether or not partial verification bias is accounted for, and correspond to false positive rates of 20% through 80%. The dashed line indicates a 'useless' test as a reference (sensitivity equal to the false positive rate). The solid line has been derived from the overlapping distributions show in Figure J4, and fits well.

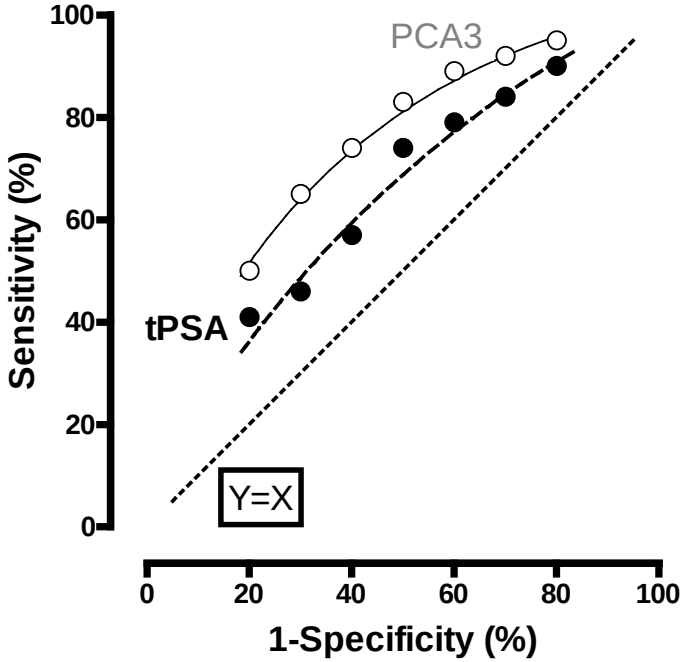


Figure J5. A fitted ROC curve for tPSA measurements, after accounting for partial verification bias.
The figure shows that the overlapping distributions provided in Figure J4 Adequately fit the observed ROC data from the literature (open circles). A simple cumulative Gaussian model can now be used to generate sensitivity at false positive rates between 20% and 80%. The PCA3 curve from Figure J3 has been included for comparison.

Interpretative analysis comparing PCA3 and tPSA performance

These parameter sets for PCA3 scores and tPSA measurements can now be used to compare their performance in identifying men who will have a positive biopsy. The following analyses rely only on the parameters presented in Figures J3 and J5 along with selected rates of cancer in the population (5%, 10% and 15%). The reported rates from the literature ranged between 10% and 30%. However, due to partial verification bias, the actually prostate cancer rates are likely to be considerably lower.

Table 1 presents a series of PCA3 score cut-off levels with accompanying false positive rates (1-specificity) and sensitivity (detection) rates. One interpretation of the false positive rate is that the proportion of negative biopsies with a negative result (specificity) will show how many biopsies could be avoided using that cut-off level. The sensitivity shows the proportion of occurring cancers that could be detected. 100% - sensitivity can be interpreted as the proportion of prostate cancers that would be missed, if that PCA3 cut-off level were to be chosen. For example, using the common PCA3 cut-off level of 35, the false positive rate is 27% (27% of men without cancer would get a biopsy), saving 73% of men without cancer having an unnecessary biopsy. The trade-off is that the detection rate is 61%, indicating that this would result in 39% of prostate cancers in the population being missed. The last two columns include the cumulative likelihood ratio (sensitivity / false positive rate) and the individual likelihood ratio (ratio of the heights of the two curves at the given value. For example, using the same score of 35 as the cut-off, the identified men will have 2.2 times the risk of cancer compared to the entire cohort of men identified with elevated tPSA levels and/or positive DRE or other findings. For men with a score of exactly 35, their risk is increased by only 16% (LR=1.16) over the cohort as a whole.

The bottom half of Table 1 presents the data in the same way, but for tPSA measurements. For example, 50% of the men who would have a negative biopsy would have a tPSA of 6 ng/mL or higher (false positive rate). Correspondingly, about 71% of the men with cancer would have levels at or above 6 ng/mL. Remember, this 71% is a conditional proportion of men with cancer among the cohort of men over age 50 identified with an initially elevated tPSA and/or with other markers. It is not the proportion of all men over age 50 with prostate cancer. The population likelihood rate indicates an increase in risk of 40%, while an individual man with a tPSA of 6 would actually see a slight reduction in risk of 15% (LR=0.85). To allow for direct comparisons, the range of cut-offs shown for the two markers cover approximately the same proportion of the overlapping distributions. The format of Table 6 makes comparisons between the two markers difficult, as neither the sensitivity nor the false positive rate is being held constant.

Table 2 compares the performance of PCA3 scores and tPSA measurement to identify men who would have a positive biopsy. The top half of the Table 2 holds the false positive rate constant, while the bottom half holds the sensitivity constant. In the last column is the difference between the two estimates (PCA3 – tPSA). When comparing the sensitivities (top half) this column contains the improvement in prostate cancer detection. When comparing the false positive rates, it contains the reduction in unnecessary biopsies. For example, assume you would like to miss no more than 10% of the existing cancers. Choose the row with 90% sensitivity (bottom half of Table 2). It shows the false positive rate would be 65.6% using PCA3 scores, but 78.2% using tPSA measurements. This means that the same proportion of cases might be

Table 1. Sensitivity, false positive rates and likelihood ratios for PCA3 and tPSA.

PCA3	1-Specificity	Saved	Sensitivity	PCa	Likelihood Ratio	
Score	(FPR)	Biopsy	(DR)	Missed	Population	Individual
≥10	77%	23%	95%	5%	1.2	0.35
≥15	62%	38%	88%	12%	1.4	0.52
≥20	50%	50%	81%	19%	1.6	0.68
≥25	40%	60%	74%	26%	1.8	0.84
≥30	33%	67%	67%	33%	2.0	1.00
≥35	27%	73%	61%	39%	2.2	1.16
≥40	23%	77%	55%	45%	2.4	1.32
≥45	19%	81%	50%	50%	2.6	1.47
tPSA	1-Specificity	Saved	Sensitivity	PCa	Likelihood Ratio	
Score	(FPR)	Biopsy	(DR)	Missed	Population	Individual
2	80%	20%	91%	9%	1.1	0.59
3	64%	36%	80%	20%	1.3	0.75
4	50%	50%	69%	31%	1.4	0.89
5	39%	61%	59%	41%	1.5	1.01
6	31%	69%	50%	50%	1.6	1.13
7	25%	75%	43%	57%	1.7	1.23
8	20%	80%	36%	64%	1.8	1.34
9	16%	84%	31%	69%	1.9	1.43

detectable while performing 12.6% fewer biopsies were PCA3 to be used instead of tPSA measurements.

Table 2. A comparison of PCA3 and tPSA measurements to identify men with prostate cancer with either the false positive rate, or the sensitivity held constant.

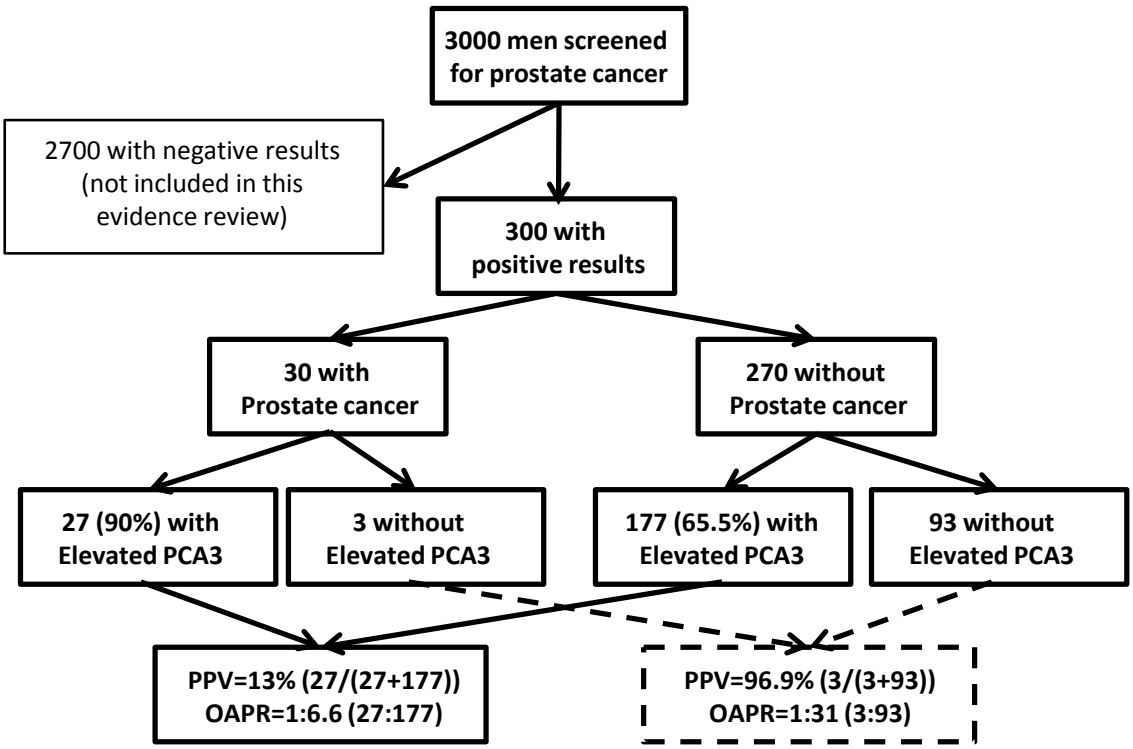
	PCA3 Measurements			tPSA Measurements		
1-Specificity (FPR)	Cut-off (Score)	Sensitivity (DR)		Cut-off (ng/mL)	Sensitivity (DR)	Improvement in PCa Detection
80%	9.2	95.8%		2.0	90.7%	5.1%
70%	12.3	92.0%		2.6	84.3%	7.7%
60%	15.8	87.2%		3.2	77.6%	9.6%
50%	20.0	81.1%		4.0	68.8%	14.0%
40%	25.1	73.7%		4.9	59.7%	14.0%
30%	32.5	63.8%		6.2	48.4%	15.4%
20%	43.4	51.6%		8.0	36.4%	15.2%
	PCA3 Measurements			tPSA Measurements		
Sensitivity (DR)	Cut-off (Score)	1-Specificity (FPR)		Cut-off (ng/mL)	1-Specificity (FPR)	Reduction in Biopsies
95%	9.9	77.7%		1.5	88.2%	10.5%
90%	13.8	65.6%		2.1	78.2%	12.6%
85%	17.3	56.3%		2.5	71.5%	15.2%
80%	20.7	48.5%		3.0	63.6%	15.1%
70%	27.7	36.2%		3.9	51.2%	15.0%
60%	35.6	26.6%		4.9	40.3%	13.7%
50%	45.0	18.9%		6.0	31.2%	12.3%

These analyses do not account for the prevalence of cancer in the cohort, so cannot determine the positive or negative predictive values. Figure J6 shows how these data can be used with cancer prevalence to determine predictive values. The figure also shows how the cohort of interest is limited to the population of men who have elevated tPSA/positive DRE. Assume the prevalence of cancer is 5%, and the PCA3 related sensitivity is chosen to be 90%. Base on Table 1, this implies a PCA3 cut-off score of 13.8 and will have a false positive rate of 65.6%. As an aside, the analysis is more confident in the performance estimates of 90% sensitivity and false positive rate than the finding that this occurs at a score of 13.8. Depending on the situation, the relevant PCA3 score may be higher or lower, depending on factors that have not yet been clarified. The flowchart first assumes that a cohort of 3,000 men is subject to prostate cancer screening and 10% are found to be 'at risk' due to elevated tPSA, positive DRE and/or other factors. The PCA3 score is then applied to this subset of 300 men, 30 of whom have prostate cancer (10%). Among the 30 men with cancer, PCA3 will be 13.8 or higher in 27 (90%). Among the 270 men without cancer, PCA3 will be elevated in 177 (65.6%). Among the 207 with a positive PCA3, the positive predictive value (PPV) is 13% (27/207). Another way to express the PPV is via odds. The PPV of 13% is equivalent to an odds of 1:6.6 (this could be read as an odds of 1 in 6.6 or as a proportion of 1 in 7.6. This is called the odds of being affected given a positive result (OAPR). Among the 96 with a lower PCA3 score, 93 will not have cancer, resulting in a negative predictive value (NPV) of 96.8%. Another way to understand the NPV is to create an odds of having cancer among those with a negative test result. This is called the odds of being affected given a negative results (OANR).

Among the 270 men without cancer, PCA3 will be elevated in 177 (65.6%). Among the 207 with a positive PCA3, the positive predictive value (PPV) is 13% (27/207). Another way to express the PPV is via odds. The PPV of 13% is equivalent to an odds of 1:6.6 (this could be read as an odds of 1 in 6.6 or as a proportion of 1 in 7.6. This is called the odds of being affected

given a positive result (OAPR). Among the 96 with a lower PCA3 score, 93 will not have cancer, resulting in a negative predictive value (NPV) of 96.8%. Another way to express the OANR is 1:31.

Figure J6. Flowchart showing the cohort of interest and how the positive and negative predictive values are computed.



The flowchart shows the performance of PCA3 testing among 300 men with positive prostate screening test results. More information is provided in the text.

Table 3 provides a summary of positive and negative predictive values for both PCA3 scores and tPSA at seven different sensitivities ranging from 50% to 95%, each with three difference cancer rates (5%, 10% and 15%). Within each of the groups with the same sensitivity, the PPV increase while the NPV decreases. Between groups, increasing sensitivity is associated with higher PPV and loser NPV rates, at the same cancer rate. When comparing across the table (PCA3 versus tPSA), both the PPV and NPV are slightly lower.

Table 3. Positive and negative predictive values for PCA3 and tPSA testing at seven selected test sensitivities, each with three different rates of prostate cancer

Sensitivity	PCa Rate	PCA3 Scores				tPSA (ng/mL)		
(DR)	(%)	FPR	PPV (OAPR)	NPV (OANR)		FPR	PPV (OAPR)	NPV (OANR)
95	5	77.7	6.0% (1:15.5)	98.8% (1:84.8)		88.2	5.4% (1:17.6)	97.9% (1:44.8)
	10	77.7	12.0% (1: 7.4)	97.6% (1:40.1)		88.2	10.7% (1: 8.4)	95.5% (1:21.2)
	15	77.7	17.7% (1: 4.6)	96.2% (1:25.3)		88.2	16.0% (1: 5.3)	93.0% (1:13.4)
90	5	65.6	6.7% (1:13.8)	98.5% (1:65.4)		78.2	5.7% (1:16.5)	97.6% (1:41.4)
	10	65.6	13.2% (1: 6.6)	96.9% (1:31.0)		78.2	11.3% (1: 7.8)	95.2% (1:19.6)
	15	65.6	19.5% (1: 4.1)	95.1% (1:19.5)		78.2	16.9% (1: 4.9)	92.5% (1:12.4)
85	5	56.3	7.4% (1:12.6)	98.2% (1:55.4)		71.5	5.9% (1:16.0)	97.3% (1:36.1)
	10	56.3	14.4% (1: 6.0)	96.3% (1:26.2)		71.5	11.7% (1: 7.6)	94.5% (1:17.1)
	15	56.3	21.0% (1: 3.8)	94.3% (1:16.5)		71.5	17.3% (1: 4.8)	91.5% (1:10.8)
80	5	48.5	8.0% (1:11.5)	98.0% (1:48.9)		63.6	6.2% (1:15.1)	97.2% (1:34.6)
	10	48.5	15.5% (1: 5.5)	95.9% (1:23.2)		63.6	12.3% (1: 7.2)	94.2% (1:16.4)
	15	48.5	22.5% (1: 3.4)	93.6% (1:14.6)		63.6	18.2% (1: 4.5)	91.2% (1:10.3)
70	5	36.2	9.2% (1: 9.8)	97.6% (1:40.4)		51.2	6.7% (1:13.9)	96.9% (1:30.9)
	10	36.2	17.7% (1: 4.7)	95.0% (1:19.1)		51.2	13.2% (1: 6.6)	93.6% (1:14.6)
	15	36.2	25.4% (1: 2.9)	92.3% (1:12.1)		51.2	19.4% (1: 4.1)	90.2% (1: 9.2)
60	5	26.6	10.6% (1: 8.4)	97.2% (1:34.9)		40.3	7.3% (1:12.8)	96.6% (1:28.4)
	10	26.6	20.0% (1: 4.0)	94.3% (1:16.5)		40.3	14.2% (1: 6.0)	93.1% (1:13.4)
	15	26.6	28.5% (1: 2.5)	91.2% (1:10.4)		40.3	20.8% (1: 3.8)	89.4% (1: 8.5)
50	5	18.9	12.2% (1: 7.2)	96.9% (1:30.8)		31.2	7.8% (1:11.9)	96.3% (1:26.1)
	10	18.9	22.7% (1: 3.4)	93.6% (1:14.6)		31.2	15.1% (1: 5.6)	92.5% (1:12.4)
	15	18.9	31.8% (1: 2.1)	90.2% (1: 9.2)		31.2	22.0% (1: 3.9)	88.6% (1: 7.8)

Table 4. Patient-specific prostate cancer risks by prior risk and by PCA3 score or tPSA measurement.

PCA3	An Individual's Prior Risks of Prostate Cancer					
Score[1]	1:19 (5%)	1:9 (10%)	1:5.7 (15%)	1:4 (20%)	1:3 (25)	1:2.3 (30%)
5	105	50	31	22	17	13
10	54	26	16	11	8.6	6.7
15	37	17	11	7.8	5.8	4.5
20	28	13	8.3	5.9	4.4	3.4
25	23	11	6.7	4.8	3.6	2.8
30	19	9.0	5.7	4.0	3.0	2.3
35	16	7.8	4.9	3.5	2.6	2.0
40	14	6.8	4.3	3.0	2.3	1.8
45	13	6.1	3.8	2.7	2.0	1.6
50	12	5.5	3.5	2.5	1.8	1.4
tPSA	Individuals Risk of PCa with Prior Risks of:					
ng/mL[1]	1:19 (5%)	1:9 (10%)	1:5.7 (15%)	1:4 (20%)	1:3 (25)	1:2.3 (30%)
3	39	18	12	8.2	6.1	4.8
4	31	15	9.2	6.5	4.9	3.8
5	26	12	7.7	5.4	4.1	3.2
6	22	11	6.7	4.7	3.5	2.7
7	20	9.4	5.9	4.2	3.1	2.4
8	18	8.4	5.3	3.7	2.8	2.2
9	16	7.7	4.8	3.4	2.6	2.0
10	15	7.0	4.4	3.1	2.3	1.8
11	14	6.5	4.1	2.9	2.2	1.7
12	13	6.1	3.8	2.7	2.0	1.6

[1] Approximate range: mean of biopsy negative minus 1 SD to mean of biopsy positive plus 0.5 SD.

To this point, all of the tables were designed to assist health care providers understand each test's performance, evaluate the trade-offs found at selected cut-off levels, and compare performance between tests. This is of less interest to an individual male who does not have a PCA3 (or tPSA) level at or above a cut-off level, but instead has a 'patient –specific' measurement that could be interpreted for that individual. Table 4 provides this information at select PCA3 and tPSA levels. There are, however, too many possibilities to provide a complete listing, but this type of information could easily be part of a computerized report. Such information could also be tailored to include other relevant risk factors such as family history of prostate cancer or race. If risk factors were present, it would be necessary to use a higher prior risk of prostate cancer (i.e., a column towards the right-hand side of the table).

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Appendix K:
Summary of the Remaining Key Questions 1 & 2 Combined Analyses

PCA3 and tPSA Elevations - Intermediate Outcome: Impact on Decisionmaking

Key Points

Ideally PCA3 would improve decisionmaking compared to tPSA by reducing unnecessary biopsies and increasing identification of prostate tumors. However, no studies were identified that reported PCA3 and tPSA levels along with specific health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

PCA3 and tPSA Elevations - Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported PCA3 and tPSA levels along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

PCA3 and tPSA Elevations - Long-term Health Outcome: Morbidity/Mortality

Key points

No studies were identified that reported PCA3 and tPSA levels along with long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

Comparator: Free serum PSA

Intermediate Outcome: Diagnostic Accuracy

Key Points

The extent of fPSA elevations were compared with PCA3 scores to determine their diagnostic accuracy to predict prostate biopsy results (cancer / no cancer).

- Area under the curve (AUC). Two studies[14, 3] reported AUC estimates for fPSA; both reported a positive difference (median 14 percent).
- Reported medians and standard deviations (SD). Only one study[13] provided sufficient data for analysis, and it did not report a logarithmic SD. The result was a z-score of 0.86, indicating that PCA3 performed better.
- Performance at a PCA3 cut-off score of 35. One study[5] reported the sensitivity and specificity of PCA3 at this cut-off that could be compared with the fPSA sensitivity. A positive effect of 14 percent higher sensitivity was reported.
- ROC Curves - Sensitivity/Specificity. Three studies[3, 5, 14] provided an ROC curve, or data representing an ROC curve for both markers. At a specificity of 50 percent, the difference in corresponding specificities (PCA3 – tPSA) was 3 percent, 18 percent, and 23 percent.
- Regression analysis. Two studies[13, 5] provided sufficient data to apply the respective regression coefficients to create a relative odds ratio (OR) between the 25th and 75th centiles of the two distributions. Both had ratios over 1 (2.88, 1.70).

Study Characteristics

A total of four studies[3, 5, 13, 14] reported PCA3 and fPSA comparisons that could be used in one or more of the matched analyses (Table 1). All of the analyses performed on the data from the four studies (100 percent) were consistent in finding the matched PCA3 estimate better at identifying positive prostate biopsies than the corresponding fPSA estimate (p=0.13, binomial distribution). However, all were rated "poor," and all only enrolled men in the 'grey zone' of tPSA. However, the association between PCA3 and fPSA is unlikely to be subject to verification bias. The generalizability of these finding should be limited to men in the "grey" area of tPSA falling between about 3 and 10 ng/mL.

Table 1. Summary results for the five analytic comparisons of PCA3 versus fPSA in matched populations of men having prostate biopsies

			Results for a matched comparison available[1]					*PCA3 > fPSA*
Author	**Year**	**Number**	**AUC**	**Mean/SD**	**PCA3>35**	**Sens/Spec**	**Reg**	**% (analyses)**
Ploussard[14]	2010	301	0.1170	-	-	18%	-	100 (2)
Aubin[3]	2010	1072	0.1740	-	-	3%	-	100 (2)
Perdona[13]	2011	218	-	0.86	-	-	2.88	100 (2)
de la Taille[5]	2011	516	-	-	17%	23%	1.70	100 (3)

[1] AUC = area under the curve for PCA3 minus the AUC of tPSA; Mean/DS = difference in separation between PCA3 scores and tPSA results, when expressed as z-scores; PCA3>35 = difference of the PCA3 minus the tPSA sensitivities at the specificity found for a PCA3 cut-off of 35; Sens/Spec = difference between PCA3 and tPSA sensitivity at a specificity of 50%; Reg = relative change in the PCA3 ORs (between the 25th and 75th centiles) and the corresponding tPSA ORs. The corresponding full analyses resulting in these summaries can be found on the following pages.

Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and fPSA: Area Under the Curve

Two studies[3, 14] satisfied inclusion criteria and relevant data are presented in Table 2. Both found that the AUC of PCA3 was greater than for fPSA. Due to the limited number of studies, no further analyses are presented.

PCA3 and fPSA: Reported Medians and Standard Deviations

Only one study satisfied the inclusion criteria and relevant data are presented in Table 3. That study[13] found a larger separation in PCA3 values between men with positive versus negative biopsies (expressed as a z-score) than the separation found for fPSA. The difference in z-scores approached one standard deviation (0.86). One additional study[5] provided some relevant data confirming the median values for both PCA3 and fPSA reported in the usable study.[13] Due to the limited number of studies, no further analyses are presented.

PCA3 and fPSA: Performance at a PCA3 Cut-Off Score of 35

Only one study[5] provided sufficient data to compare PCA3 sensitivity with the sensitivity of fPSA at the specificity defined by the PCA3 cut-off score of 35 (Table 4). That study reported the PCA3 sensitivity to be 17 percent higher than the corresponding fPSA sensitivity at the same (1-specificity) rate of 24 percent Due to the limited number of studies, no further analyses are presented.

PCA3 and fPSA: ROC Curves - Sensitivity / Specificity

Three studies[3, 5, 14] provided sufficient data to compare PCA3 sensitivity versus fPSA sensitivity at (1-specificity) rates of 20 percent through 80 percent (Table 5). Two of the studies[5, 14] found PCA3 sensitivity to be higher than the fPSA sensitivity across the range of (1-specificity) rates examined. The third study[5], found the advantage only held at lower (1-specificity) levels. No study reported the sensitivity of fPSA to be higher than PCA3 at any (1-specificity) level. Due to the limited number of studies, no further analyses are presented.

Table 2. Comparing PCA3 levels and free PSA (fPSA) measurements in matched studies via AUC analysis to correctly diagnose prostate cancer, as defined by a positive needle biopsy

Author	Year	Number	Initial Bx	PCA3 AUC	fPSA AUC	Difference[2]	P-value[3]
Ploussard[14]	2010	301	0	0.6880	0.5710	0.1170	-
Aubin[3]	2010	1072	0	0.6930	0.5190	0.1740	0.04

Bx = biopsy, AUC = area under the curve, '-' = no value reported

[1] Individual quality of study based on QUADAS scoring

[2] AUC (PCA3) – AUC (tPSA), all comparisons were between all subjects, regardless of repeat / initial biopsy status

[3] Reported p-value for the comparison of the two AUCs computed among the same set of men

Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

Table 3. Comparison of PCA3 and free PSA (fPSA) differences in central estimates in men with positive and negative prostate biopsy results, after accounting for study-specific variability in measurements

			PCA3 Scores				fPSA Results (ng/mL)				
			Median for Bx		Pooled	Z_{PCA3}[1]	Median for Bx		Pooled	Z_{fPSA}[1]	$Z_{PCA} - Z_{fPSA}$
Author	Year	N	Pos	Neg	Log SD		Pos	Neg	Log SD		
Perdona, S[13]	2011	218	72.0	22.0	0.4264	1.21	15.0	17.0	0.1543	0.35	0.86
de la Taille, A[5]	2011	516	50.0	18.0	-	-	14.0	17.8			

Pos = prostate biopsy positive, Neg = prostate biopsy negative
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.
[1] Z score = (log (Pos median) – log (Neg median)) / pooled log SD

Table 4. A comparison of PCA3 and fPSA in identifying a positive prostate biopsy among matched studies: difference in sensitivities at the fixed specific associated with the commonly used PCA3 score cut-off of 35

			Prostate Biopsy		PCA3 score		fPSA[2]	Difference
Author	Year	Number	Initial	Positive	1-Spec (%)	Sens (%) A	Sens (%) B	(A-B) (%)
de la Taille[5]	2011	516	-	40.0	24.0	64.0	47.0%	17%

Spec=specificity (1-specificity=false positive rate), Sens = sensitivity (detection rate).
[1] Individual quality of study based on QUADAS scoring
Sensitivity for fPSA elevation at the same false positive rate (1-specificity) found for a PCA3 score at a cut-off of 35.
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

Table 5. Matched studies of PCA3 and fPSA testing performance to identify positive biopsy men

			PCA3 Sensitivity (Difference)[1] at PCA3 (1-Specificity) Rates of:						
Author	Year	Number	20%	30%	40%	50%	60%	70%	80%
Aubin[3]	2010	1072	49 (13)	60 (13)	68 (10)	74 (3)	79 (0)	85 (0)	94 (1)
Ploussard[14]	2010	301	40 (9)	56 (17)	71 (23)	80 (18)	83 (14)	89 (11)	93 (3)
de la Taille[5]	2011	516	57 (21)	71 (20)	77 (18)	85 (22)	89 (19)	93 (16)	95 (9)
Median			**49 (13)**	**60 (17)**	**71 (18)**	**80 (18)**	**83 (14)**	**89 (11)**	**93 (3)**

[1] (PCA3 sensitivity – fPSA sensitivity) when (1-specificity) is held constant at values ranging from 20% to 80%.
Bx = prostate biopsy, Corr = Correlation coefficient, OR = odds ratio, raw = as observed, adj = after adjustment for other marker
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and fPSA: Regression Analysis

To be included in this analysis, studies would have reported the odds ratio (OR) for each marker, when that marker was assumed to be a continuous variable. The coefficients were used to compute the ratio of the ORs at the 25th and 75th centiles for each marker. This ratio of ORs for PCA3 will then be divided by the corresponding ratio for fPSA. Values greater than 1 indicate PCA3 provides more discrimination than fPSA. This normalization also allows for comparisons between studies, where the coefficient is dependent on the range of fPSA values studied.

Three studies[3, 5, 13] reported results of regression analysis separately for PCA3 and for fPSA elevations in the same population of men to be included in these analyses. Only two of the studies[5, 13] provided sufficient data to complete the analysis (Table 6). Both found the ratio of ORs over the inter-quartile range to be greater for PCA3 than for fPSA. All three studies included in this analysis restricted tPSA to <10 ng/mL.

Two specific measures were sought regarding the independence of PCA3 and fPSA as markers for prostate biopsy status. Bivariate correlations (parametric or non-parametric) and results of logistic regression. Other markers may also be included in the regression model (e.g., prostate volume). If both PCA3 and fPSA coefficients remain essentially constant after adjusting for the other marker (and possibly, additional markers), this can be taken as evidence that the two markers together are more predictive that either alone.

Only two studies[3, 13] provided some information regarding independence of PCA3 and fPSA (Table 7). None reported information on correlation coefficients. Both reported the univariate and multivariate ORs for PCA3 which indicated little change when other makers were added. Similar results were found for tPSA, but in one of the studies[3], fPSA was not included in the 'best' predictive model.

Table 6. Comparison of modeled univariate continuous odds ratios (OR) for PCA3 and fPSA in matched studies

			PCA3 Odds Ratio (OR)				fPSA Odds Ratio (OR)				Ratio
Author	**Year**	**N**	**report**	**@25th**	**@75th**	**Ratio^A**	**report**	**@75th**	**@25th**	**Ratio^B**	**(A/B)**
Perdona[13]	2011	218	1.030	16	70	4.93	0.935	20	12	1.71	2.88
Aubin[3]	2010	1072	1.019	9	35	1.63	0.924	-	-	-	-
de la Taille[5]	2011	516	1.020	13	52	2.16	0.970	20*	12*	1.28	1.70

* Centiles from Perdona[13] with no changes (medians identical); both excluded patients with tPSA ≥10 ng/mL.
Bx = prostate biopsy, Corr = Correlation coefficient, OR = odds ratio, raw = as observed, adj = after adjustment for other marker
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

Table 7. Measures of independence of PCA3 and fPSA in identifying men having a positive biopsy finding in matched studies

			Corr (PCA3/fPSA)		PCA3 OR	fPSA OR	Other relevant findings
Author	**Year**	**Number**	**Bx Pos**	**Bx Neg**	**(raw, adj)**	**(raw, adj)**	
Perdona[13]	2011	218	-	-	1.030/1.030	0.936/0.968	fPSA not included in 'best' model
Aubin[3]	2010	1072	-	-	1.019/1.015	0.935/0.934	Model includes PCA3 values

Bx = prostate biopsy, Corr = Correlation coefficient, OR = odds ratio, raw = as observed, adj = after adjustment for other marker
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and fPSA Diagnostic Accuracy

PCA3 and fPSA GRADE Strength of Evidence: Insufficient

- Risk of Bias: LOW
  fPSA is not highly correlated with tPSA and, therefore, the partial verification bias, and sampling bias identified for the tPSA analyses are not expected to bias the fPSA analyses.
- Consistency: CONSISTENT
  All analyses for all four studies found PCA3 to perform better than fPSA.
- Directness: INDIRECT
  The ultimate outcome of interest is long-term morbidity / mortality.
- Precision: IMPRECISE
  A formal analysis of precision (e.g., confidence intervals) was not able to be computed due to the matched nature of our analyses, the lack of original data and the limited number of included studies.

PCA3 and fPSA Intermediate Outcome: Impact on Decisionmaking

Key Points

No studies were identified that reported PCA3 and fPSA levels along with health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

PCA3 and fPSA Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported PCA3 and fPSA levels along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

PCA3 and fPSA Long-Term Health Outcome: Morbidity/mortality

Key points

No studies were identified that reported PCA3 and fPSA levels along with other long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

Comparator: Serum PSA Density (PSAD)

Intermediate Outcome: Diagnostic Accuracy

Key Points

PSAD measurements were compared with PCA3 scores to determine their diagnostic accuracy to predict prostate biopsy results (cancer/no cancer). Measures included in the analyses are the sensitivity, specificity (or the false positive rate equal to 1-specificity), and positive and negative predictive values.

- Area under the curve (AUC). Only two studies[5, 11] reported AUC estimates for PSAD and PCA3 in the same population. Both found the better performance for PCA3 (AUC differences of 0.07 and 0.03).
- Reported medians and standard deviations (SD). Only one study[11] provided sufficient data for analysis, and it did not report a logarithmic SD. The difference, reported as z-scores of 0.5, was in favor of PCA3.
- Performance at a PCA3 cut-off score of 35. One study[5] reported the sensitivity and specificity of PCA3 at this cut-off that could be compared with the PSAD sensitivity. A positive effect of 17 percent higher sensitivity was reported.
- ROC Curves - Sensitivity / Specificity. Two studies[5, 11] provided an ROC curve, or data representing an ROC curve for both markers. At a specificity of 50 percent, the differences in corresponding specificities (PCA3 – PSAD) were 9 percent, and 12 percent.
- Regression analysis. Only one study[11] provided data regarding PCA3 and PSAD regression analysis, but there was insufficient to create a relative odds ratio (OR) between the 25th and 75th centiles of the two distributions.

Study Characteristics

Two studies[5, 11] reported PCA3 and PSAD comparisons that could be used in one or more of the matched analyses (Table 8). All of the analyses were consistent in finding the matched PCA3 estimate better identifying positive prostate biopsies than the corresponding PSAD estimate (p=0.50, binomial distribution).

Table 8. Summary results for the five analytic comparisons of PCA3 versus PSAD in matched populations of men having prostate biopsies

			Results for a matched comparison available[1]					PCA3 > PSAD
Author	Year	Number	AUC	Mean/SD	PCA3>35	Sens/Spec	Reg	% (analyses)
de la Taille[5]	2011	516	0.0720	-	17%	12%	-	100% (3/3)
Ochiai[11]	2011	105	0.0342	0.51	-	9%	-	100% (3/3)

[1] AUC = area under the curve for PCA3 minus the AUC of tPSA; Mean/DS = difference in separation between PCA3 scores and tPSA results, when expressed as z-scores; PCA3>35 = difference of the PCA3 minus the tPSA sensitivities at the specificity found for a PCA3 cut-off of 35; Sens/Spec = difference between PCA3 and tPSA sensitivity at a specificity of 50%; Reg = relative change in the PCA3 ORs (between the 25th and 75th centiles) and the corresponding tPSA ORs. The corresponding full analyses resulting in these summaries can be found on the following pages.

Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and PSAD: Area Under the Curve

Two studies[5, 11] satisfied inclusion criteria and relevant data are presented in Table 9. Both found that the AUC of PCA3 was greater than for PSAD, but the smaller difference found for

one study[11] did not reach statistical significance. Due to the limited number of studies, no further analyses are presented.

Table 9. Comparing PCA3 levels and PSA density (PSAD) in matched studies via AUC analysis to correctly diagnose prostate cancer, as defined by a positive needle biopsy

Author	Year	Number	Initial Bx	PCA3 AUC	PSAD AUC	Difference[2]	P-value[3]
Ochiai[11]	2011	105	81%	0.8507	0.8164	0.0342	0.67
de la Taille[5]	2011	516	100%	0.7610	0.6890	0.0720	0.023

Bx = biopsy, AUC = area under the curve, '-' = no value reported
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.
1 Individual quality of study based on QUADAS scoring
2 PCA3 AUC – PSAD AUC
3 Reported p-value for the comparison of the two AUCs computed among the same set of men

PCA3 and PSAD: Reported Medians and Standard Deviations

The same two studies[5, 11] satisfied the inclusion criteria and relevant data are presented in Table 10. In one, the log standard deviation was estimated using the range of results.[11] The difference in z-scores was 0.51, indicating a better separation between men with positive and negative biopsies for PCA3 compared to PSAD. In the other study,[5] it was not possible to estimate the log standard deviation. Due to the limited number of studies, no further analyses are presented.

Table 10. Comparison of PCA3 and PSA density (PSAD) in central estimates in men with positive and negative prostate biopsy results, after accounting for study-specific variability in measurements

			PCA3 Scores				PSAD Results (ng/mL)				
			Median for Bx		Pooled	Z_{PCA3}[1]	Median for Bx		Pooled	Z_{PSAD}[1]	$Z_{PCA} - Z_{PSAD}$
Author	Year	N	Pos	Neg	Log SD		Pos	Neg	Log SD		
Ochiai[11]	2011	105	59.5	14.2	0.3489	1.78	0.38	0.17	0.2740	1.27	0.51
de la Taille[5]	2011	516	50.0	18.0	-	-	0.15	0.11	-	-	-

Bx = prostate biopsy, Pos = prostate biopsy positive, Neg = prostate biopsy negative
Z score = (log (Pos median) – log (Neg median)) / pooled log SD
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and PSAD: Performance at a PCA3 Cut-Off Score of 35

One study[5] provided sufficient to computer PCA3 sensitivity with the sensitivity of PSAD at the specificity defined by the PCA3 cut-off score of 35 (Table 11). That study reported the PCA3 sensitivity to be 17 percent higher than the corresponding PSAD sensitivity at the same (1-specificity) rate of 24 percent. Due to the limited number of studies, no further analyses are presented.

Table 11. A comparison of PCA3 and PSAD in identifying a positive prostate biopsy among matched studies: difference in Sensitivities at the fixed specific associated with the commonly used PCA3 score cut-off of 35

			Prostate Biopsy		PCA3 score		PSAD[2]	Difference
Author	Year	Number	Initial	Positive	1-Spec (%)	Sens (%) A	Sens (%) B	(A-B) (%)
de la Taille[5]	2011	516	-	40.0	24.0	64.0	47.0%	17%

Spec=specificity (1-specificity=false positive rate), Sens = sensitivity (detection rate)
[1] Individual quality of study based on QUADAS scoring
[2] Sensitivity for PSAD elevation at the same false positive rate (1-specificity) found for a PCA3 score at a cut-off of 35.
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and PSAD: ROC Curves - Sensitivity / Specificity

Two studies[5, 11] provide sufficient data to compare PCA3 sensitivity versus PSAD sensitivity at (1-specificity) rates of 20 percent through 80 percent (Table 12). Both found PCA3 sensitivity to be higher than the PSAD sensitivity across the range of (1-specificity) rates examined, with the exception of one study at a very high specificity.[11] Due to the limited number of studies, no further analyses are presented.

Table 12. Matched studies of PCA3 and PSAD Testing performance to identify positive biopsy men

			PCA3 Sensitivity (Difference)1 at PCA3 (1-Specificity) Rates of						
Author	Year	Number	20%	30%	40%	50%	60%	70%	80%
de la Taille[5]	2011	516	57 (13)	71 (15)	77 (15)	85 (12)	89 (3)	93 (3)	95 (0)
Ochiai[11]	2011	105	74 (- 3)	87 (3)	92 (3)	97 (9)	98 (4)	100 (0)	100 (0)
Median			**66 (5)**	**79 (9)**	**85 (9)**	**91 (10)**	**93 (4)**	**97 (2)**	**98 (0)**

[1] (PCA3 sensitivity – PSAD sensitivity) when (1-specificity) is held constant at values ranging from 20% to 80%.
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and PSAD: Regression Analysis

Only one study[11] reported results of the selected analyses regarding the independence of PCA3 and PSAD in predicting prostate biopsy results. They combined PCA3 and PSAD results as categorical variables and showed a higher sensitivity for the combination than for either marker alone; but only at specificities of 70 percent or higher. Due to the limited number of studies, no further analyses are presented.

PCA3 and PSAD Intermediate Outcome: Diagnostic Accuracy

- Risk of Bias: LOW.
  PSAD is not highly correlated with tPSA and, therefore, the partial verification bias, and sampling bias identified for the tPSA analyses are not expected to bias the PSAD analyses
- Consistency: CONSISTENT
  All analyses for both studies found PCA3 to perform better than PSAD.
- Directness: INDIRECT
  The ultimate outcome of interest is long-term morbidity / mortality.
- Precision: IMPRECISE
  A formal analysis of precision (e.g., confidence intervals) was not able to be computed due to the matched nature of our analyses, the lack of original data, and the limited number of included studies.

GRADE Strength of Evidence: Insufficient

PCA3 and PSAD - Intermediate Outcome: Impact on Decisionmaking

Key Points

No studies were identified that reported PCA3 and PSAD levels along with health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

PCA3 and PSAD - Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported PCA3 and PSAD levels along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

PCA3 and PSAD - Long-Term Health Outcome: Morbidity/Mortality

Key Points

No studies were identified that reported PCA3 and PSAD levels along with long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

Comparator: Externally Validated Nomogram (EVN)

PCA3 and EVN Intermediate Outcome: Diagnostic Accuracy

Key points

Externally validated nomograms were compared with PCA3 scores to determine their diagnostic accuracy to predict prostate biopsy results (cancer / no cancer). Measures included in the analyses are the sensitivity, specificity (or the false positive rate equal to 1-specificity), and positive and negative predictive values.

- Area under the curve (AUC). Only two studies[2, 13] reported AUC estimates for EVN and PCA3 in the same population. Both found the better performance for PCA3 (AUC differences of 0.01 and 0.11).
- Reported medians and standard deviations (SD). One study[13] provided sufficient data for analysis, and did not report a logarithmic SD. The differences, reported as z-scores, were 0.52 and 0.22; in favor of PCA3.
- Performance at a PCA3 cut-off score of 35. No studies reported results in this manner.
- ROC Curves - Sensitivity / Specificity. Two studies[2, 13] provided an ROC curve, or data representing an ROC curve for both markers. At a specificity of 50 percent, the differences in corresponding specificities (PCA3 – PSAD) were 4 percent and -4 percent.
- Regression analysis. No studies reported results in this manner.

Study Characteristics

Three studies[2, 11, 13] reported PCA3 and EVN comparisons that could be used in one or more of the matched analyses (Table 13). Comparisons were made to both Chun's nomogram and the PCPT model. The following sections provide detailed information about the five analyses performed and the specific findings.

Table 13. Summary results for the five analytic comparisons of PCA3 versus externally validated nomograms (EVN) in matched populations of men having prostate biopsies

				Results for a matched comparison available[1]					PCA3 > EVN
Author	Year	Quality[1]	Number	AUC	Mean/SD	PCA3>35	Sens/Spec	Reg	% (analyses)
Perdona[13]	2011	Poor	218	0.113	0.52	-	4%	-	100% (3/3)
Ochiai[11]	2011	Poor	105	-	-	-	-4%		0% (0/1
Ankerst[2]	2008	Poor	443	0.012	0.22	-	-	-	100% (2/2)

[1] AUC = area under the curve for PCA3 minus the AUC of tPSA; Mean/DS = difference in separation between PCA3 scores and tPSA results, when expressed as z-scores; PCA3>35 = difference of the PCA3 minus the tPSA sensitivities at the specificity found for a PCA3 cut-off of 35; Sens/Spec = difference between PCA3 and tPSA sensitivity at a specificity of 50%; Reg = relative change in the PCA3 ORs (between the 25th and 75th centiles) and the corresponding tPSA ORs. The corresponding full analyses resulting in these summaries can be found on the following pages.

Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and EVN: Area Under the Curve

Two studies[2, 13] satisfied inclusion criteria and relevant data are presented in Table 14. Both found that the AUC of PCA3 was greater than for EVN, but the smaller difference found for one study[2] did not reach statistical significance. Due to the limited number of studies, no further analyses are presented.

Table 14. Comparing PCA3 and EVN scores in matched studies via AUC analysis to correctly diagnose prostate cancer, as defined by a positive needle biopsy

Author	Year	Quality1	Number	Initial Bx	PCA3 AUC	EVN AUC	Difference[1]	P-value[2]
Perdona[13]	2011	Poor	218	61%	0.8280	0.7150	0.1130	0.003
Ankerst[2]	2008	Poor	443	81%	0.6650	0.6530	0.0120	NS

Bx = biopsy, AUC = area under the curve, '-' = no value reported
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.
1 PCA3 AUC – EVN AUC
2 Reported p-value for the comparison of the two AUCs computed among the same set of men

PCA3 and EVN: Reported Medians and Standard Deviations

One study[13] satisfied the inclusion criteria and relevant data are presented in Table 15. That group used the 'Chun's risk' as well as the 'PCPT risk' nomograms. Both found that PCA3 was better than either of the externally validated nomograms. Due to the limited number of studies, no further analyses are presented.

Table 15. Comparison of PCA3 and externally validated nomograms (EVN) in central estimates in men with positive and negative prostate biopsy results, after accounting for study-specific variability in measurements

				PCA3 Scores				EVN Scores				$Z_{PCA} - Z_{EVN}$
				Median for Bx		Pooled	Z_{PCA3}[1]	Median for Bx		Pooled	Z_{EVN}[1]	
Author	Year	N	EVN	Pos	Neg	Log SD		Pos	Neg	SD		
Perdona[13]	2011	218	Chun's "risk"	72.0	22.0	0.4264	1.21	54	41	18.9	0.69	0.52
Perdona[13]	2011	218	PCPT "risk"	72.0	22.0	0.4264	1.21	54	39	15.2	0.99	0.22

Bx = prostate biopsy. Pos = prostate biopsy positive, Neg = prostate biopsy negative; Bx = prostate biopsy, SD = standard deviation
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.
1 Z score = (log (Pos median) – log (Neg median)) / pooled log SD

PCA3 and EVN: Performance at a PCA3 Cut-Off Score of 35

No studies were identified that provided relevant data.

PCA3 and EVN: ROC Curves - Sensitivity / Specificity

Two studies[2, 13] provide sufficient data to compare PCA3 sensitivity versus EVN sensitivity at (1-specificity) rates. Both used the risk algorithm by Chun.[27] One[13] provided data for specificities of 20 percent through 80 percent (Table 16) and found PCA3 to be better. The second study only reported results for 20 percent through 40 percent and found the EVN only slightly better. Due to the limited number of studies, no further analyses are presented.

Table 16. Matched studies of PCA3 and EVN testing performance to identify positive biopsy men

			PCA3 Sensitivity (Difference)[1] at PCA3 (1-Specificity) Rates of						
Author	Year	Number	20%	30%	40%	50%	60%	70%	80%
Perdona[13]	2011	218	70 (23)	79 (27)	82 (20)	88 (4)	97 (4)	100 (4)	100 (2)
Ochiai[11]	2011	105	44 (- 7)	56 (- 6)	67 (- 4)				

1 (PCA3 sensitivity – EVN sensitivity) when (1-specificity) is held constant at values ranging from 20% TO 80%
Shaded rows indicate studies focusing on the 'grey zone' of tPSA.

PCA3 and EVN: Regression analysis

No studied provided a comparison of an externally validated model with / without PCA3.

PCA3 and EVN - Intermediate Outcome: Diagnostic Accuracy

- Risk of Bias: LOW.
  EVNs often include tPSA and, therefore, the partial verification bias, and sampling bias identified for the tPSA analyses may have an impact. However, none of the models actually used tPSA (which are most subject to bias) and thus biasing the EVN analyses is not expected.
- Consistency: CONSISTENT
  All analyses for both studies found PCA3 to perform better than fPSA.
- Directness: INDIRECT
  The ultimate outcome of interest is long-term morbidity / mortality; the subject of Key Question 3.
- Precision: IMPRECISE
  A formal analysis of precision (e.g., confidence intervals) was not able to be computed due to the matched nature of our analyses, the lack of original data, and the limited number of included studies.

GRADE Strength of Evidence: Insufficient

PCA3 and EVN - Intermediate Outcome: Impact on Decisionmaking

Key Points

No studies were identified that reported PCA3 and EVN results along with health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

PCA3 and EVN - Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported PCA3 and EVN results along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

PCA3 and EVN - Long-Term Health Outcome: Morbidity/Mortality

Key points

No studies were identified that reported PCA3 and EVN results along with long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

Comparator: Multivariate Models including PCA3 and tPSA

Study Characteristics

Three studies[3, 5, 13] reported multivariate models (logistic regression) that included both tPSA elevations and PCA3 scores. Only one of these[5] provided results for both a base model and the base model plus PCA3 scores. The base model include the man's age, DRE (categorical), tPSA (continuous), and prostate volume (continuous); all were statistically significant ($p<0.01$). PCA3 score as a continuous variable was then included. The coefficients in the base model were essentially unchanged with all point estimates being within the 95 percent CI of the base model estimates and all remaining statistically significant. The p-value associated with PCA3 measurements was <0.001. This implies that the PCA3 scores adds independent information.

However, there are several limitations to the study. Neither the tPSA nor PCA3 measurements were reported to have been transformed. An underlying assumption of logistic regression is that continuous variables are reasonably Gaussian and this was most likely violated by the modeling. Second, the authors provided no information regarding the change in sensitivity at fixed specificities. Rather, they provided an increase in predictive accuracy, a difficult to interpret estimate.

Multivariate Models Including PCA3 and tPSA - Outcome: Diagnostic Accuracy

GRADE Strength of Evidence: Insufficient

- Risk of Bias: LOW.
  Multivariate models often include tPSA and, therefore, the partial verification bias, and sampling bias identified for the tPSA analyses may have an impact.
- Consistency: INCONSISTENT
  Only one study was available, so consistency could not be examined.
- Directness: INDIRECT
  The ultimate outcome of interest is long-term morbidity / mortality; the subject of Key Question 3.
- Precision: IMPRECISE
  A formal analysis of precision (e.g., confidence intervals) was not able to be computed due to the matched nature of our analyses, the lack of original data, and the limited number of included studies.

Multivariate Models Including PCA3 and tPSA - Intermediate Outcome: Impact on Decisionmaking

Key Points

No studies were identified that reported the multivariate model results along with health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

Multivariate Models Including PCA3 and tPSA - Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported the multivariate model results along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

Multivariate Models Including PCA3 and tPSA - Long-term Health Outcome: Morbidity/Mortality

Key points

No studies were identified that reported the multivariate model results along with long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

Comparator: Complexed PSA (cPSA)

PCA3 and cPSA - Intermediate Outcome: Diagnostic Accuracy

No studies were identified that provide matched data for PCA3 and cPSA among men with positive and negative initial or repeat prostate biopsy results.

GRADE Strength of Evidence: Insufficient

PCA3 and cPSA - Intermediate Outcome: Impact on Decisionmaking

Key Points

No studies were identified that reported PCA3 and cPSA levels along with health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

PCA3 and cPSA - Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported PCA3 and cPSA levels along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

PCA3 and cPSA - Long-term Health Outcome: Morbidity/Mortality

Key points

No studies were identified that reported PCA3 and cPSA levels along with long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

Comparator: Total PSA Doubling Time (DT) and Total PSA Velocity (PSAV)

PCA3 and DT/PSAV - Intermediate Outcome: Diagnostic Accuracy

No studies were identified that provide matched data for PCA3 and DT/PSAV results among men with positive and negative initial or repeat prostate biopsy results.

GRADE Strength of Evidence: Insufficient

PCA3 and DT/PSAV - Intermediate Outcome: Impact on Decisionmaking

Key Points

No studies were identified that reported PCA3 and DT/PSAV results along with health outcomes that support a reduction in unnecessary biopsies (false positives) with maintenance or improvement in cancer detection.

GRADE Strength of Evidence: Insufficient

PCA3 and DT/PSAV - Intermediate Outcome: Biopsy-Related Harms

Key Points

No studies were identified that reported PCA3 and DT/PSAV results along with health outcomes related to harms of biopsy.

GRADE Strength of Evidence: Insufficient

PCA3 and DT/PSAV - Long-term Health Outcome: Morbidity/Mortality

Key points

No studies were identified that reported PCA3 and DT/PSAV results along with long-term health outcomes, such as morbidity, mortality or quality of life.

GRADE Strength of Evidence: Insufficient

QUADAS Ratings of Individual Studies

The detailed results of assessment of quality of individual studies addressing KQ1 and KQ2 are presented in Table F-1 (Appendix F).

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