Characteristics of studies

Characteristics of included studies

Bollito 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Consecutive cohort. Mixed initial and repeat biopsy. Repeat reported separately. Men receiving PCA3 test and referred for repeat biopsy based on persistent PSA elevation. Men with positive DRE and/or ASAP on initial biopsy excluded.A*ssumed this means all DRE normal.*
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	3 centres Italian: Turin, Orbassano. Milan
Was risk of underlying risk of Cancer in men in study population representative?	No
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	PCA3 Clinical : age, PSA, %fPSA No mention of blinding.

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	14-18 peripheral and transition zone cores - taken by experienced urologist. All specimens evaluated by experienced pathologist with an interest in uropathology. No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Biopsy after PCA3 assessment. Assume < 1 yr. 6 out of 515 excluded due to inconclusive biopsy result
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

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Busetto 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Inclusion: a first random TRUS-guided prostate biopsy that was negative for PC or high-grade prostatic intraepithelial neoplasm and a PSA level of 4-10 ng/mL.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	Italy? University hospital Rome. Prospective cohort.
Was risk of underlying risk of Cancer in men in study population representative?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3; Clinical: *Age, PSA and DRE;* multiparametric MRI with magnetic resonance spectroscopic imaging, diffusion-weight imaging, and dynamic contrast-enhanced imaging. No mention of blinding of results

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test- MRI

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	The biopsy protocol was a 10-core. (2 cores from the basal portion, lateral and paramedial; 2 from the midgland, lateral and paramedial; and 1 from the apex, on each side of the gland). In those cases with areas described by MRSI, DWI, and DCEI as suspicious for PC, 2 additional TRUS-guided cores were taken from each site considered abnormal.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Yes

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	PCA3 test before biopsy. 171 consecutive patients in the study. Two patients (1.2%) were excluded from the analysis because of insufficient PSA messenger RNA to evaluate the PCA3 test. Another 2 patients (1.2%) were excluded because of the impossibility of performing mMRI, and 4 patients (2.3%) declined informed consent.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

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European cohort

Patient Selection

A. Risk of Bias	
Patient Sampling	Men with one or two previous negative prostate biopsies (>=6 cores performed at >=3 mo prior to enrolment) scheduled for repeat biopsy were enrolled. Prospective.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	6 European centres. Prospective cohort.
Was risk of underlying risk of Cancer in men in study population representative?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3 Progensa Clinical: Total and fPSA,number of previous biopsies, age, prostate volume No mention of blinding

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	At least 10 standardized periph zone. Bx taken by an experienced physician. The specimens were evaluated by the pathologist at each site.No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	Unclear

Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Biopsy Immediately after blood and urine samples taken.470 subjects, 467 urine samples adequate for PCA3, 463 had conclusive biopsy results.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

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Gittelman 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Participants were men without PCa with 1 or more previous negative prostate biopsy session who were recommended by their physician for repeat biopsy
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	Geographically diverse, community based urology clinics, group health organizations and academic institutions in the United States. Prospective cohort
Was risk of underlying risk of Cancer in men in study population representative?	Yes

Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3 Progensa Assay. Laboratory personnel were blinded to subject clinical status, and sPSA and biopsy results. Clinical variables: age, DRE result, family history of PCa, race and number of previous negative biopsy sessions.

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	12 core or greater TRUS biopsy. Each specimen was evaluated at the site pathology facility according to institutional procedures. All pathologists were blinded to PCA3 assay and other test results
Is the reference standards likely to correctly classify the target condition?	No

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Test order = blood, urine, biopsy – usually all within 24 hrs. Bx within 7 days of blood and urine within 7 days of blood samples. 6/474 excluded due to < 50 yrs. Not enough to affect results.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

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Goode 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Retrospective review of notes. Mixed biopsy population. Repeat reported separately. Men with no known personal history of prostate cancer who underwent a prostate biopsy because of an elevated PSA level, abnormal digital rectal exam (DRE), or abnormal previous prostate biopsy-prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP).
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	1 centre. US
Was risk of underlying risk of Cancer in men in study population representative?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3 Clinical: prostate volume, patient age, patient race, family history, and digital rectal exam status. **PSA not included.** The laboratories processing the blood and urine specimens and the pathologists examining the biopsy cores were unaware of the patients' clinical status.

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	12 core TRUS. Pathologists examining the biopsy cores were unaware of the patients' clinical status.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	Yes
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Retrospective design. Unclear selection and timing.
Was there an appropriate interval between index test and reference standard?	Unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	High risk

Notes

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Lazzeri 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	a negative first biopsy but persistent suspicion of PCa who were scheduled for repeat biopsy according to the European Association of Urology guidelines of increasing and/or persistently elevated PSA, suspicious DRE, atypical small acinar proliferation and high grade prostate intraepithelial neoplasia
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes

Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability		
Patient characteristics and setting	University hospital Milan. Prospective cohort	
Was risk of underlying risk of Cancer in men in study population representative?		Yes
Are there concerns that the included patients and setting do not match the review question?		Low concern

Index Test

Index tests	phi Clinical: PSA, prostate volume, and DRE, %fPSA and PSA density No mention of blinding

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Ambulatory transrectal ultrasonography guided prostate biopsies according to a standardized institutional scheme to obtain the highest detection rate. 24 core saturation Bx. Range of cores 12-26. Specimens were processed and evaluated by a single experienced genitourinary pathologist. Pathologist blinded but not clear about person performing biopsy.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Blood sample was drawn at the time of repeat biopsy.8/230 samples not analyzed according to p2PSA product insert claimed stability informa. 22 analysed
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

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Panebianco 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	first random TRUS-guided prostate biopsy negative for prostate adenocarcinoma or high-grade prostate intraepithelial neoplasm; persistent elevated PSA levels (total PSA ≥ 4 ng/ml and <10 ng/ml) and negative digital rectal examination (DRE). *Assumed this means all DRE normal*.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Italian hospital ? Rome. Prospective cohort
Was risk of underlying risk of Cancer in men in study population representative?	No
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	PCA3 MRI

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test- MRI

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	10-core laterally directed (two cores from the basal portion lateral and paramedial, two from the midgland lateral and paramedial, and one from the apex, on each side of the gland for each patient, plus 3 additional biopsies from other areas suspicious for PCa at MRSI)
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Tests before repeat biopsy. Assume < 1 yr. 41/43 participants had informative PCA3 results.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

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Pepe 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	All men had negative family history, abnormal DRE, PSA 4.1-10 or 2.6-4. All caucasian.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Italy ? catania Unclear whether prospective/retrospective cohort
Was risk of underlying risk of Cancer in men in study population representative?	No
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	PCA3 Clinical; PCPT nomogram -Age, race, PSA, DRE, family history, previous negative biopsy No mention of blinding

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear

Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Transperineally, saturation biopsy. At least 12 in the posterior zone of each lobe and 2-3 in the transition zone Median 30, range 24-38. No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	PCA3 test 3-10 days before biopsy. All patients had adequate PCA3.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

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Perdona 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Men referred for prostate biopsy because of abnormal PSA and/or suspicious DRE.Mixed and repeat but repeat reported separately. No PSA > 10 ng/mL.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	3 centre Italian study - Naples, Catanzaro. Prospective.
Was risk of underlying risk of Cancer in men in study population representative?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3 Chun: age, PSA, DRE, previous Bx, prostate volume. PCPT: race, age, PSA, fam Hx, DRE & previous Bx. Multivariate: AGE, transrectal ultrasound (TRUS) abnormalities, prostate volume, history of previous biopsy, family history of PCa No mention of blinding

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	systematic, laterally directed,? transrectal ? >= 12-core, median 12 (IQR 12-16). Evaluated by an experienced pathologist at each site. No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	PCA3 test immediately before biopsy. 84 men with repeat Biopsy - no other details.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	

Porpiglia 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	Negative initial Bx – 12 cores. Persistently elevated PSA levels, **and/or** positive digital rectal examination
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability		
Patient characteristics and setting	Italy - Orbassano. Prospective	
Was risk of underlying risk of Cancer in men in study population representative?		Yes
Are there concerns that the included patients and setting do not match the review question?		Low concern

Index Test

Index tests	PCA3 & Phi Clinical: DRE, age, **NOT PSA** No mention of blinding for PCA3 / PSA lab personnel. mp-MRI: diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) MRI. The radiologist was blinded to the pathologist's biopsy reports and to the biomarker results (but ? knew clinical status).

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High concern

Comparator test- MRI

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Two dedicated urologists blinded to the mp-MRI reports and to the biomarkers results performed all RB. 18 or 24 core depending on prostate volume. No extra cores for MRI result. May have been affected by clinical findings but better controlled than many other studies. Histological examination was conducted by a dedicated uropathologist, who was blinded to the biomarkers and to the mp-MRI results, according to a standardised protocol.
Is the reference standards likely to correctly classify the target condition?	No

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Were the same number & pattern of cores taken in all participants?	Yes
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	PCA3, phi and MRI Prior to repeat biopsy- asume < 1 yr.4 /174 excluded due anterior Ca
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

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REDUCE placebo

Patient Selection

A. Risk of Bias	
Patient Sampling	Cohort of patients from placebo arm of REDUCE trial. Followed for 4 years. Selection into this study depended on trial site being able to process urine sample for PCA3. Only scheduled biopsies used. Low risk population as "for cause" biopsies excluded.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	REDUCE trial. Multi centre international study. Prospective cohort within.
Was risk of underlying risk of Cancer in men in study population representative?	No
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3 Progensa Assay. PCA3 Operators were blinded with respect to biopsy results and study arm (placebo vs dutasteride). Not quite clear how being used in algorithm . Clinical variables used; life expectancy, DRE findings, PSA level, prostate volume, number of previous negative PBxs

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	10 core transrectal biopsies. Biopsies were read at the central pathology laboratory (CPL, which processed the majority, 94%, of biopsies).No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	Unclear
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	At time of repeat Biopsy?. Assume < 1 yr. 48/ 172 with informative PCA3 not included in model in Tombal due to missing covariates.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

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Scattoni 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Candidates for initial or repeat PBx at 2 tertiary care institutions.Indication for repeat Bx ASAP, plurifocal HGPIN , PSA 2-15 and/or positive DRE.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability		
Patient characteristics and setting	Consecutive, prospective cohort	
Was risk of underlying risk of Cancer in men in study population representative?		Yes
Are there concerns that the included patients and setting do not match the review question?		Low concern

Index Test

Index tests	PCA3, phi Clinical: age, DRE, volume, PSA, f/tPSA

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard'	Unclear
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Ambulatory transrectal ultrasound guided PBx according to a standardized institutional saturation scheme. at least 14 to 24 biopsy cores. Mean 18.7 ± 3.2. No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	95 repeat patients. A blood sample was drawn at biopsy just before prostatic manipulations.Urine sample just before Bx.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

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Sciarra 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	First negative prostate biopsy to cancer & HGPIN , persistent total PSA > 4 ng/mL and negative DRE. *Assumed this means all DRE normal.* Consecutive patients who were referred to the Department of Urology. Randomly assigned (1:1) to PCA3 only or PCA3 plus MRI before repeat biopsy.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes

Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	
Was risk of underlying risk of Cancer in men in study population representative?	No
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	PCA3 MRI

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test- MRI

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	All TRUS and biopsies were performed using an end-fire ultrasonographic transducer and biopsy gun with an 18-gauge needle (Esaote Technos MP with a C10-5 transducer. laterally directed 10-core. In cases with areas described by MRI as being suspicious for cancer, two additional cores were taken from each area that was labelled abnormal. All biopsies were performed in the department by a single physician (M.C.) with a long experience of this procedure. Histological assessments were carried out blind to the results of the MRI. ? blind to PCA3?

Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	2nd biopsy within 90 days of 1st biopsy. Unclear timing of PCA3 test but at or after 1st biopsy. 180 cases with first negative random biopsy and persistent total PSA > 4 ng/ml. 12 indaequate PCA3 sample Baseline PCA3. 168 cases entered trial.

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

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Stephan 2013

Patient Selection

A. Risk of Bias	
Patient Sampling	Unclear – described as both case-control and cohort. Patients enrolled prospectively and retrospectively. 1362 men; 681 patients (50%) were included for initial biopsy and 280 patients (21%) were scheduled for a repeated biopsy, and for the remaining 401 patients (29%) this information was missing.tPSA results between 1.6 and 8.0g/L (calibration against a WHO PSA reference material)
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	4 centres in Germany and France
Was risk of underlying risk of Cancer in men in study population representative?	Unclear
Are there concerns that the included patients and setting do not match the review question?	Unclear concern

Index Test

Index tests	phi - p2PSA Clinical: Age, prostate volume, DRE, tPSA, %fPSA. Participants and investigators were blinded to p2PSA results and the personnel involved in testing (p2PSA?) were blinded to patients' clinical information

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	transrectal ultrasound (TRUS)-guided needle biopsy. 10 -22 cores. According to standard clinical practice routinely used at each site. No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	All blood samples were obtained before any manipulations involving the prostate and at least 3 weeks after a digital rectal examination (DRE). Patient flow unclear.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

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Wu 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Consecutive retrospective study.Indications for repeat prostate biopsy were based on suspicious DRE, persistently elevated PSA, previous suspicious histology (such as high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation) and/or patient preference.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Were men selected into study on basis of cancer risk such as on PSA range, DRE MRI etc.	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	I centre. San Francisco, US
Was risk of underlying risk of Cancer in men in study population representative?	Yes
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	PCA3 Clinical : own nomogram PSA, PSAD, **TRUS** and DRE Chun nomogram: *Age,DRE,previous bx, vol* PSA, PSAD No mention of blinding.

Intervention test

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Comparator test - clinical & PSA

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Unclear
Were the comparator test results interpreted without knowledge of the results of the intervention test?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	transrectal ultrasound (TRUS). >=12 (two cores from each sextant of the prostate are taken plus additional cores from suspicious areas by TRUS and/or anterior prostate cores). All performed by same clinician. No mention of blinding.
Is the reference standards likely to correctly classify the target condition?	No
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Were the same number & pattern of cores taken in all participants?	No
Was the reference standard performed & results interpreted without knowledge of the results of the comparator tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	High concern

Flow and Timing

A. Risk of Bias	
Flow and timing	103 out of 188 patients with full data included (54.7%). PCA3 before repeat Bx - time gap not given. Assume < 1yr
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

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Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables