National Institute for Health and Care Excellence

FINAL

Prostate cancer: diagnosis and management

[E] Evidence review for following up people at risk of prostate cancer

NICE guideline NG131

Evidence reviews

May 2019

These evidence reviews were developed by the NICE Guideline Updates Team

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RQ8: Following-up people at increased risk of prostate cancer

Review question

What is the most clinically- and cost-effective follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy?

Introduction

A negative prostate biopsy and/or negative MRI does not definitively exclude the presence of cancer. People who have had a negative biopsy or MRI may still have prostate cancer. Factors that might indicate undetected prostate cancer include a raised prostate specific antigen (PSA), abnormal digital rectal examination (DRE), abnormal results of other PSA-based tests, such as free PSA to total PSA expressed as a percentage (free-to-total PSA%), PSA density and PSA velocity and new biomarkers, such as the prostate cancer gene 3 (PCA3) assessed prior to initial biopsy.

This review aims to identify studies reporting accuracy data for measures that can help simulate strategies to follow-up people who have a raised PSA, negative MRI and/ or negative biopsy as specified in Table 1. For full details of the review protocol, see appendix A.

PICO table

Table 1: PICO table

Population	• People who have a raised PSA and negative MRI • People who have a raised PSA and negative biopsy
Intervention	• Individual or repeated PSA tests and calculations derived from them (including tPSA, fPSA, %fPSA, PSAD) • Digital rectal examination • MRI
Reference standard	• Biopsy (TRUS or TPM) • Radical prostatectomy specimen • Clinical emergence of cancer (follow up at least 10 years)
Outcomes	Diagnostic accuracy • Sensitivity and specificity • Likelihood ratios

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy

Clinical evidence

Included studies

A systematic literature search for diagnostic cross-sectional studies and systematic reviews of diagnostic cross-sectional studies with no date limit yielded 5,032 references. These were screened on title and abstract, with 396 full-text papers ordered as potentially relevant diagnostic cross-sectional studies or systematic reviews of diagnostic cross sectional studies. Diagnostic cross-sectional studies were excluded if they did not meet the criteria of enrolling patients with at least one previously negative biopsy and persistent suspicion of prostate cancer. Studies were also excluded if they did not include the index tests and the reference standard as specified in the protocol. To ensure that only studies reflecting current practice were included, the committee set out additional criteria for studies investigating the diagnostic accuracy of multiparametric MRI. The criteria stated that the:

- MRI protocols should use at least 1.5 Tesla magnet, include diffusion weighted imaging (with the highest b value of at least 800s/mm^2)
- MRI scoring should be clearly stated (using either PIRADS or LIKERT scoring system)

Studies were further excluded at data extraction if it was not possible to calculate sensitivity and specificity.

Thirty eight papers were included after full text screening. Several systematic reviews were identified, however only 1 was included as it provided 2x2 contigency tables for some of the included studies. The study was included as partially applicable evidence.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches, which included articles up to August 2018, returned 212 references for this review question, and these were screened on title and abstract. No additional relevant references were found.

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G.

Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion

Summary of clinical studies included in the evidence review

Prostate cancer antigen 3 urinary assay

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
Barbera (2012)	Study location Italy Study dates January 2010 and March 2012	Sample size 177 participants Mean age (SD) Median (range) 64 (48-74) years PSA ng/ml 74 participants had serum PSA >10ng/ml 99 between 4-10ng/ml 4 between 2.6-4ng/ml Number of previous biopsies at least one prior biopsy Time since last biopsy Not reported	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination An elevated PSA >10ng/ml	Prostate Cancer Gene 3 Cut off of 20 and 35	Systematic prostate biopsy Performed transperineally
Busetto (2013)	Study location Italy Study dates March 2010 and July 2012	Sample size 171 participants Mean age (SD) 66.4 (5.3) years PSA ng/ml 6.8 (1.6)ng/ml	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer A persistently elevated or rising serum total PSA level Between 4-10ng/ml	Prostate Cancer Gene 3 3 cut off - 27,35 and 50 Digital rectal examination (DRE)	Systematic TRUS biopsy
Gittelman (2013)	Study location USA Study dates Not reported	Sample size 466 participants Mean age (SD) to add from supplement PSA ng/ml to add from supplement	At least one negative TRUS biopsy 50 years and older	Prostate Cancer Gene 3	TRUS biopsy and MP-MRI biopsy

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
		PSA density, ng/ml/ml to add from supplement Mean prostate volume to add from supplement			
Haese (2008)	Study location Six European centres - Germany, France, The Netherlands, Belgium and Austria Study dates Between August and July 2007.	Sample size 463 participants Mean age (SD) 64.4 (6.6) years PSA ng/ml Mean 8.9 (7.5)ng/ml Number of previous biopsies 331 participants had 1 biopsy 126 participants had 2 biopsies	At least one negative TRUS biopsy	Prostate Cancer Gene 3 The PCA3 was calculated as [PCA3 mRNA]/[PSA mRNA]x1000	TRUS biopsy
Kaufmann (2016)	Study location Germany Study dates Between 2008-2014	Sample size 49 patients Mean age (SD) 65 (5.6) years PSA ng/ml 10 (4.4) ng/ml PSA density, ng/ml/ml 0.22 (0.12) ng/ml/g Number of previous biopsies 1.7 (0.9) biopsies median interval of time between the first and last PSA assay 6 (3) months		Prostate Cancer Gene 3 cut off of 25 and 35	TRUS biopsy
Marks (2007)	Study location Nothern American Sites	Sample size 233 participants	At least one negative TRUS biopsy	Prostate Cancer Gene 3	Systematic TRUS biopsy

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
	Study dates between April 2004 and January 2006	Mean age (SD) 64 years (7) PSA ng/ml 7.4 (4.3)ng/ml Mean prostate volume 49 (29)ml	An elevated PSA 2.5ng/ml or greater		
Merola (2015)	Study location Italy Study dates Between November 2009 and May 2011	Sample size 407 participants Mean age (SD) reported separately for cancer/non cancer groups cancer median 71 years (sd27) non cancer median 69 years (sd31) PSA ng/ml reported separately for cancer/non cancer groups cancer median 7.53ng/ml (sd4.88) non cancer median 7.34 ng/ml(sd5.87)	At least one negative TRUS biopsy An elevated PSA Suspicious DRE	Prostate Cancer Gene 3 Total PSA unable to calculate 2x2 for this test %fPSA unable to calculate 2x2 for this test	Saturation prostatic biopsy
Pepe (2011)	Study location Italy Study dates From October 2009 to September 2011	Sample size 102 participants Mean age (SD) median age 64.5 yrs; range: 58-71 yrs)	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination	Prostate Cancer Gene 3 PSA ratio	TRUS biopsy The prostate biopsy protocol included a median of 12 cores in the posterior zone of each lobe (apex, median zone and base of the gland) beginning parasagittally to reach the outer edges of the gland (lateral margins) and 2-3 cores in the transition zone

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
Pepe (2012)	Study location Italy Study dates January 2010 to May 2011	Sample size 118 participants Mean age (SD) median 62.5 years (no range or sd) PSA ng/ml Median PSA 8.5 ng/ml (3.7-24ng/ml) Time since last biopsy 9 months	At least one negative TRUS biopsy Abnormal digital rectal examination All patients had a negative DRE An elevated PSA PSA> 10ng/ml, PSA values between 4.1 - 10 or 2.6-4ng/ml with free/total PSA </= 25% and </= 20% respectively.	Prostate Cancer Gene 3 From 3-10 days prior to performing SPBx, first catch urine samples were collected following DRE, and processed to quantify PCA3 and PSA mRNA concentrations using the PROGENSA PCA3 assay	Systematic prostate biopsy performed transperineally using a tru-cut 18 gauge needle supplied with a biplanar transrectal probe under sedation and antibiotic prophylaxis
Porpiglia (2014)	Study location Italy Study dates Between March 2011 and April 2013	Sample size 170 participants Mean age (SD) Median age (iqr) 65 years (60-70)	At least one negative TRUS biopsy Positive Digital rectal examination	mp-MRI All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil. Functional information was obtained by DWI and dynamic contrast enhanced MRI. Total PSA %fPSA All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California)16 after	Random Biopsy under TRUS

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
				processing with a Unicel Dxl 800 Immunoassay System analyzer (Beckman Coulter). Prostate health index	
Remzi (2010)	Study location Austria Study dates Not reported See Haese et al	Sample size 463 participants	presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE Suspicious imaging results low %free PSA Follow up biopsy	Prostate Cancer Gene 3	Prostate biopsy - not specified
Wu (2012)	Study location USA Study dates not declared	Sample size 103 participants Mean age (SD) 63.5 years (7.4) PSA ng/ml 11.0 ng/ml (8.5)	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE	Prostate Cancer Gene 3 PSA density	Systematic TRUS biopsy

Multiparametric MRI

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
Abd-Alazeez (2014)	Study location UK Study dates not stated	Sample size 54 participants Median age (Range) 64 years (39-75) PSA ng/ml median, range - 10 (2-23) Number of previous biopsies Between 1 and 3 biopsies Median Prostate volume 53 (19-136)	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA	MP-MRI MRI comprised of T2 weighted, diffusion weighted and dynamic contrast enhanced imaging with either 1.5T and 3.0T . diffusion b values - 0,150,500 and 1000. Positive MRI - PIRADS Score 3 and above Positive MRI - PIRADS score 4 and above For clinically significant disease	Transperineal Template Mapping Biopsy minimum number of samples was 20
Boesen (2018)	Study location Denmark Study setting No details provided Study dates Betweeb September 2011 to September 2013 Sources of funding No financial support	Sample size 289 participants %female n/a Median age (Range) 64 years (59-67) PSA ng/ml Median Range - 12.0 (8.3 - 19)ng/ml PSA density, ng/ml/ml Median (range) - 0.19 (0.13-0.29) Number of previous biopsies median range - 2 (1-6) (unclear if this is months or years)	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination A previous abnormal TRUS image No patients had previously undergone MPMRI	mp-MRI PSA density Threshold - >0.15ng/ml/ml MRI guided/influenced bioPSY T2 weighted, diffusion weighted image ad dynamic contrast enhanced was performed prior to rebiopsy. DWI b values - 0, 100,800,1400s/mm2	TRUS guided biopsy

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
Lista (2015)	Study location Spain	Sample size 150 Mean age (SD) 66.2 (5) PSA ng/ml 11.3 (9.6) Time since last biopsy 3 - 6 months	At least one negative TRUS biopsy An elevated PSA >4 ng/ml	mp-MRI	TRUS biopsy
Simmons (2017)	Study location UK Study dates 11 January 2012 to 29 January 2014.	Sample size 249 participants Mean age (SD) 62 (7) years PSA ng/ml 6.8 (4.8–9.8) ng/ml/ml Number of previous biopsies 1 (1–2) Median Prostate volume 37.0 (26.8–50.0)	At least one negative TRUS biopsy	mp-MRI Using a 3 T magnetic field strength scanner with a pelvic-phased array coil. Magnetic resonance imaging sequences included T1- weighted, T2-weighted, diffusion weighting with high b-value (b¼2000) sequence and apparent diffusion coefficient map using multiple b-values (b¼0, 150, 500, 1000) and dynamic contrast enhancement with gadolinium Positive MRI - PIRADS Score 3 and above	Transperineal Template Mapping Biopsy
Tsivian (2017)	Study location USA Study dates 3 year period beginning in 2011	Sample size 50 patients Median age (Range) 65 (61-69) years PSA ng/ml Median (IQR) - 7.1 (5.1-	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA	mp-MRI	Transperineal Template Mapping Biopsy

Short Title	Study details	Sample characteristics	Inclusion criteria	Index test (s)	Reference standard (s)
		13.6) Number of previous biopsies 1 - 23 participants 2/more - 27 participants			

PSA and PSA derivatives

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
Auprich (2012)	Study location USA Study setting hospital Study dates Between July 2008 and July 2009 Sources of funding None declared	Sample size 127 participants Mean age (SD) reported as median range 63 (50-70) years PSA ng/ml median (range) 5.3 (3.2-45.5)	presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE Patient aged 70 years or below	Total PSA %fPSA	Systematic TRUS biopsy included both 12/14 cores
Benecchi (2006)	Study location Italy Study setting No details provided Study dates Between January 2001 and June 2005 Sources of funding No funding details	Sample size 312 men Median age (Range) 66.3 years (range 45–86). PSA ng/ml Median 7.1 (range 0.74–47.2 mg/l). median interval of time between the first and last	Abnormal digital rectal examination PSA >4.0ng/ml Men with six or more cores and with at least three consecutive in 547 or more days before biopsy entered the	Total PSA PSAV The PSA velocity was calculated according to the indication of Khan and Carter; for instance, with three PSA, the equation is 0.5 {[(PSA2- PSA)/elapsed time in years)]+[(PSA3-	TRUS biopsy

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
	provided	PSA assay 959 days (range 547–3723) Median PSA slope 0.403 ng/ml/year (range -8.7to 18.07)	study.	PSA2)/elapsed time in years)]}, where PSA1 is the first of the three measurements, PSA2 the second and PSA3 the third;elapsed time refers to time between the two measurements PSA slope PSA slope was obtained fitting the line of least squares (PSA versus time) for each patient.	
Busetto (2013)	Study location Italy Study setting Not reported Study dates March 2010 and July 2012 Sources of funding None disclosed	Sample size 171 participants Mean age (SD) 66.4 (5.3) years PSA ng/ml 6.8 (1.6)ng/ml	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer A persistently elevated or rising serum total PSA level Between 4-10ng/ml	Prostate Cancer Gene 3 3 cut off - 27,35 and 50 mp-MRI Digital rectal examinatio (DRE)	Systematic TRUS biopsy
Chen (2011)	Study location China Study setting Hospital Study dates From April 1999 to February 2008	Sample size 212 men Mean age (SD) 66.59 (9.92) years PSA ng/ml 6.34 (1.66) ng/ml PSA density, ng/ml/ml 0.182 (0.203) ng/ml/ml	Inclusion criteria At least one negative TRUS biopsy Abnormal digital rectal examination An elevated PSA PSA between 4 and 10.0 ng/ml	Total PSA Serum tPSA and free PSA (fPSA) were measured using TPSA-RIACT and FPSA-RIACT kits (CIS-Bio International, France), respectively %fPSA PSAV For the determination of PSAV, the latest three values of tPSA were	TRUS biopsy TRUS-guided prostate biopsy was performed using an 18-G needle. The number of core biopsy specimens in the first and second TRUS-guided prostate biopsy was the same. The number was between 8 and 14.

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
				obtained, and PSAV was calculated using linear regression PSA density	
Gnanaprag asam (2016)	Study location United Kingdom Study dates Between 2013 and 2015	Sample size 279 people Mean age (SD) 66 years (range 45-80)	At least one negative TRUS biopsy	Prostate health index	Transperineal Template Mapping Biopsy
Horinaga (2002)	See Ohigashi (2005) for details as this was an associated study				
Keetch (1996)	Study location USA Study setting No details provided Study dates Beginning July 1989 Sources of funding None declared	Sample size 327 participants Mean age (SD) 68 (6) years PSA ng/ml Median 6.8 ng/ml (SIR 1.9)	Abnormal digital rectal examination An elevated PSA A previous abnormal TRUS image At least 2 prostate biopsies	PSA density was calculated by dividing the serum PSA at initial biopsy by the TRUS determined prostate volume at initial biopsy PSA slope PSA slope was determined by subtracting the PSA valueat the inintial screening visit from that at the most recent biopsy divided by the years between these 2 values	TRUS biopsy
Lazzeri (2012)	Study location Italy Study setting Not declared Study dates June 2010 and June 2011 Sources of funding No financial support	Sample size 222 participants Mean age (SD) 63.9 years (7.1) PSA ng/ml Median (range) 7.6ng/ml, (0.3-46.4) PSA density, ng/ml/ml	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination presence of high grade	Total PSA %fPSA Prostate health index Beckman-Coulter phi using the formula p2PSA/fPSA x square root of tPSA p2PSA,%p2PSA	TRUS biopsy

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
	declared, however Unicel Dxl 800 Immuniassay Aystem analyzer p2PSA ([-2]proPSA) reagents were provided by Beckman Coulter Inc and Beckman Coulter Italy	Median (range) 0.11 (0.02-0.91) ng/ml/ml	prostate intraepithelial neoplasia presence of atypical small acinar proliferation	derived using the formula (p2PSA pg/ml/fPSA ng/ml x 1,000)x100	
Lee (2012)	Study location Korea Study setting Hospital Study dates From January 2007 to December 2010 Sources of funding None declared	Sample size 151 participants Mean age (SD) benign group - 64.82±6.59 years cancer group - 66.27±5.47 years PSA density, ng/ml/ml 0.177±0.083 ng/ml/ml Time since last biopsy 9.48±5.05 months	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination An elevated PSA	PSA ratio The PSA change ratio was defined as the ratio of post-biopsy total serum PSA to baseline total serum PSA at the initial biopsy PSA density PSA density was calculated as baseline serum PSA divided by total prostate volume, and post-biopsy serum PSA blood sampling was done 60 minutes after the last biopsy core was attained. Free/Total PSA ratio PSA ratio	TRUS biopsy
Michielsen (1998)	Study location Belgium Study dates between October 1996 and September 1997 Sources of funding None declared	Sample size 59 people Mean age (SD) 67 years (no SD) PSA ng/ml 8.8 ng/ml (no SD) Mean prostate volume 44 ml (no SD)	Serum PSA below 15ng/ml Aged 57-83 years	PSA density PSA transition zone	Systematic TRUS biopsy

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
Murray (2014)	Study location Chile Study setting No details provided Study dates January 2006 and December 2010 - people withut pCA were followed untill dec 2014 Sources of funding No details provided	Sample size 164 participants %female N/A Mean age (SD) 65.1 (8.5) years PSA ng/ml Median (range) - 6.18ng/ml (4.95 - 9.26) Median fPSA 15% IQR - 11%-19% Median Prostate volume 56ml (IQR 42-67ml)	Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination An elevated PSA PSA > 4ng/ml PSA velocity of >0.75ng/ml/year	%fPSA Chun's Normogram Total PSA AND %free PSA were measured before the DRE using the automatic system for total PSA and %FPSA	TRUS biopsy all biopsies were standard 12 core.
Murray (2016)	Study location Chile Study setting Hospital Study dates January 2006 to December 2014 Sources of funding No funding details provided		Abnormal digital rectal examination An elevated PSA PSA > 4ng/ml PSA velocity of >0.75ng/ml/year	%fPSA Chun's Normogram	TRUS biopsy
Ohigashi (2005)	Study location Japan Study setting No details provided Study dates Between October 1997 and January 2000 Sources of funding No details provided	Sample size 75 participants Mean age (SD) 67.6 years (6.7) PSA ng/ml Mean (sd) - 7.58(1.37) PSA density, ng/ml/ml 0.208 (0.076) ng/ml/cm3 Mean fPSA 0.189 (0.107)	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination PSA > 4ng/ml PSA between 4 and 10.0 ng/ml	Total PSA PSA density Free/Total PSA ratio	TRUS biopsy

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
Porpiglia (2014)	Study location Italy Study setting Hospital Study dates Between March 2011 and April 2013 Sources of funding None declared	Sample size 170 participants Mean age (SD) Median age (iqr) 65 years (60-70)	At least one negative TRUS biopsy Positive Digital rectal examination	mp-MRI All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil. Functional information was obtained by DWI and dynamic contrast enhanced MRI. Total PSA %fPSA All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California)16 after processing with a Unicel DxI 800 Immunoassay System analyzer (Beckman Coulter). Prostate health index	Random Biopsy under TRUS
Remzi (2003)	Study location Austria Study setting Not detailed Study dates January 1997 to January 2001	Sample size 820 patients Mean age (SD) 68years (8.5) PSA ng/ml Mean 6.4 ng/ml (1.8) PSA density, ng/ml/ml	At least one negative TRUS biopsy PSA between 4 and 10.0 ng/ml	Total PSA PSA density PSA transition zone Free/Total PSA ratio	TRUS biopsy

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
	Sources of funding Not declared	0.156 ng/ml/ml (0.007) Time since last biopsy 6 weeks			
Shaida (2009)	Study location UK Study setting Hospital Study dates between 1997 and 2002 Sources of funding None declared	Sample size 67 participants	At least one negative TRUS biopsy An elevated PSA >20ng/ml	PSAV PSA density	Trus biopsy
Shimbo (2009)	Study location Japan Study setting Hospital Study dates From January 2004 to December 2005 Sources of funding None declared	Sample characteristics Sample size 77 cases Mean age (SD) 72.4+6.6 years PSA ng/ml Initial tPSA (ng/ml) 7.2+2.7 tPSA (ng/ml) 10.2+3.8 PSA density, ng/ml/ml Mean 0.36+0.22ng/ml	At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA in a range between 4 and 20 ng/ml	%fPSA %Free/tPSA was calculated from dividing free PSA by tPSA PSA doubling time	TRUS biopsy
Yilmaz (2015)	Study location Turkey Study setting Hospital Study dates between 2005 and 2011 Sources of funding None declared	Sample size 605 participants Mean age (SD) median age (IQR) - 65years (59-71) PSA ng/ml 6.3 (5.1-7.8)ng/ml Mean prostate volume 49.9cm3 (36.2-69.1) Mean fPSA	At least one negative TRUS biopsy tPSA between 2.5ng/ml and 10.0ng/ml Negative digital rectaln examination (defined as benign)	%fPSA Different cut off points - 10%, 15%, 20%, 25%	Systematic TRUS biopsy 12 core

Short Title	Study Details	Sample Characteristics	Inclusion Criteria	Index Tests	Reference Standard
		1.1 (IQR - 0.8-1.5)ng/ml			

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

Economic evidence

Included studies

Standard health economic filters were applied to the clinical search strategy for this question. Details are provided in appendix C. In total, 667 records were returned, of which 666 could be confidently excluded on sifting of titles and abstracts. The remaining study was ordered to be reviewed, and it was found not to be relevant, as it did not include economic evaluation.

Excluded studies

Details of studies excluded after consideration at the full-text stage are provided in appendix H.

Economic model

The committee identified this question as its top priority for original modelling. There has been substantial variability of practice, especially since MRI became a routine part of the diagnostic pathway, with little certainty about the long-term follow-up of people with apparently negative findings. For full details of the methods and results of the analysis, please see the health economic appendix.

Methods

We developed a lifetime Markov model with 3-monthly cycle to explore the follow-up of people who have a raised PSA, negative MRI and/or negative prostate biopsy. A follow-up protocol was defined as a strategy that combined screening tests over a follow-up time and, if the screening test is positive, a further diagnostic procedure was required. Prostate cancer diagnosis can only be determined by a positive prostate biopsy. The model adopted a patient perspective for outcomes and an NHS and PSS perspective for costs, in line with Developing NICE guidelines (2014). Health outcomes and costs were discounted applying a discount rate at 3.5% per year.

The simulated population enter the decision problem with a negative diagnosis, though some people are **true negative** (no cancer) and some are **false negative** (undetected cancer). People with no cancer are at risk of developing prostate cancer (false negative); at some point, those with undetected prostate cancer are likely to be diagnosed and hence become **true positive** cases (detected prostate cancer). The model assumes that prostate biopsies are perfectly specific; hence, a false positive state is not required. People with diagnosed or undiagnosed cancer are risk stratified into states representing low-risk (clinically non-significant) prostate cancer, intermediate-risk and high-risk localised disease and metastatic disease. The model simulates symptomatic or incidental findings (e.g., urinary symptoms that may indicate prostate pathology and skeletal pain that may indicate metastatic disease) as triggers that would lead to a potential diagnosis regardless of other markers. The model assumes that undiagnosed metastatic disease would be identified when people developed symptoms.

Clinically significant prostate cancer was defined as Gleason score ≥ 3+4 (i.e. any score of 7 or more). The terms used for health states in the model follow the cancer risk categories

recommended by NICE (CG175 2014). A schematic depiction of the model structure is provided in Figure 1.

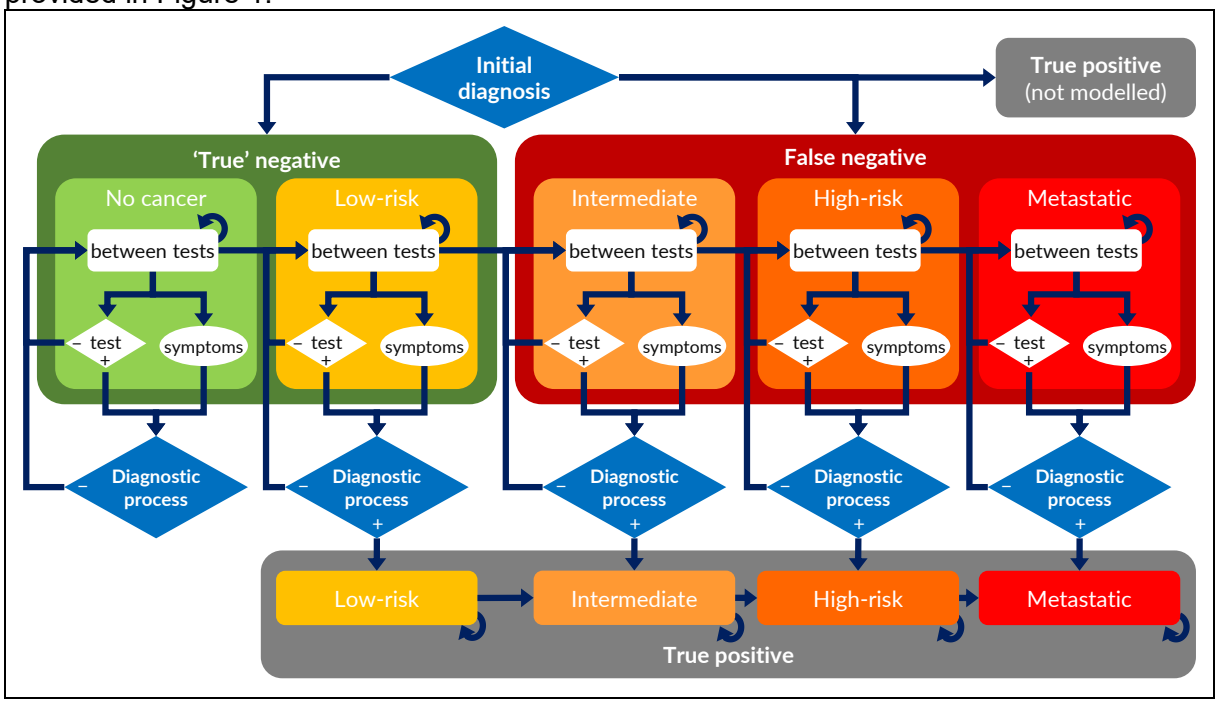


Figure 1: Schematic depiction of original health economic model

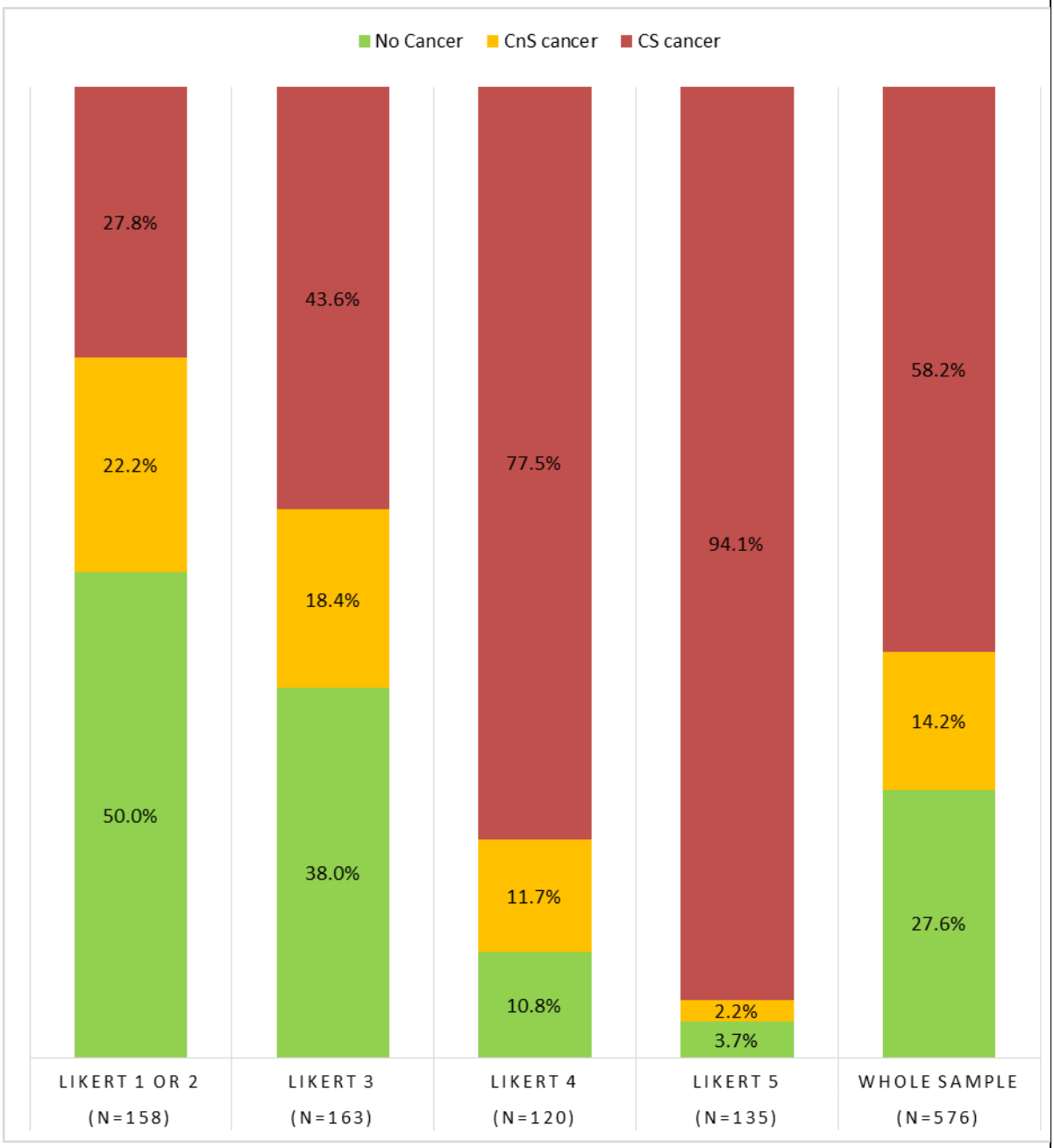
The base-case modelled cohort comprises men at age 66 with suspected prostate cancer and prior negative findings on mpMRI and/or 1 or 2 biopsies. Therefore, the model addresses different baseline populations based on diagnostic history, and each has a different starting distribution of people with true negative and false negative status, as shown in Table 2. Evidence to calculate these probabilities was predominantly drawn from evidence review D of this update, which investigates the optimal diagnostic pathway for people with suspected prostate cancer, with particular reliance on PROMIS (Ahmed et al., (2017) and PRECISION (Kasivisvanathan et al., 2018).

Table 2: Baseline distribution of the modelled population based on previous diagnostic tests

MRI Likert score	Prevalence of clinically significant PCa	No. of previous negative biopsies	Baseline distribution of the modelled population		
			No cancer	Clinically non-significant	Clinically significant
1 or 2	27.8%	0	50.0%	22.2%	27.8%
		1	68.1%	18.1%	13.8%
		2	78.4%	14.6%	7.0%
3	43.6%	1	61.1%	25.7%	13.2%
		2	68.2%	26.0%	5.8%
4	77.5%	1	36.8%	37.3%	25.9%
		2	46.6%	45.3%	8.1%
5	94.8%	1	39.4%	20.2%	40.4%
		2	61.3%	28.1%	10.6%
no MRI	58.2%	1	59.9%	26.6%	13.5%
		2	68.4%	27.4%	4.2%

The prevalence of clinically significant prostate cancer was based on that reported in PROMIS, as the committee indicated that the eligibility criteria for the study are

representative of the population of interest for this question. The prevalence of clinically non-significant prostate cance was also obtained from PROMIS, Figure 2.



The whole sample estimates is the average of all Likert scores assigned for those who did not receive mpMRI in our model.

CnS: Clinically non-significant; CS: Clinically significant

Figure 2: The prevalence of clinically significant and non-significant prostate cancer obtained from PROMIS

The simulated follow-up strategies were formed based on screening and diagnostic tests that the committee considered clinically meaningful. They ranged from the least intensive strategies, i.e. no screening and waiting for symptoms, to the most rigorous ones i.e. performing a transperineal template mapping (TPM) biopsy, assumed to be perfectly sensitive, for all people. In the base case, all follow-up strategies stopped when the modelled cohort reached 75 years, which the committee advised was a realistic upper threshold (mostly because the average person would be unlikely to be considered for radical therapy

on diagnosis beyond this age). However, this was subject to sensitivity analysis, recognising that people can still receive radical treatment at an age more than 75 in clinical practice.

The natural history of prostate cancer is simulated using data derived from key UK or European studies. Prostate cancer specific mortality is taken from STAMPEDE where James et al. (2016) reported findings on the overall survival for people with metastatic prostate cancer. A study by Gnanapragasam et al. (2016) analysed UK registry data on people with localised prostate cancer and reported disease specific mortality according to risk groups. We used their findings to derive the progression probabilities within people with diagnosed prostate cancer. The rates of adverse events associated with prostate cancer primary treatments were sourced from ProtecT (Donovan et al., 2016) for localised disease and from STAMPEDE for metastatic prostate cancer. Findings on metastases risk rates from different risk groups of localised prostate cancer were reported in the Scandinavian Prostate Cancer Group 4 trial (SPCG4), by Bill-Axelson et al. (2014), where participants were assigned either to radical prostatectomy or watchful waiting. The watchful waiting represented a non-curative strategy. Thus, it appeared to be relevant to source the progression probabilities in our undiagnosed population.

In this analysis, people with undiagnosed and diagnosed metastatic prostate cancer are at risk of disease specific mortality obtained from the standard of care arm and the docetaxel arm in STAMPEDE, respectively.The base case model deploys disease specific mortality as a proportional hazard to general mortality. The model seems to fit the data better than the scenario where disease specific mortality was assigned a constant probability.

Results

The screening tests included in the follow-up strategies simulated in our model were obtained from our clinical review that identified a number of tests. GRADE tables in Appendix G show these tests with their accuracy data. Optimal follow-up strategies were identified for different sub-populations. Table 3 shows the results of the base case analysis where all possible strategies were included.

The strategy where people receive TPM biopsy at the beginning of follow-up appeared to be the most optimal strategies in the majority of the sub-populations. However, this type of biopsy was assumed to be perfectly sensitive in the model, which may not be the case in clinical practice. In addition, it may lead to overdiagnosis, causing potential harms that the base case model may underestimate. The committee also advised that it was not feasible to adopt this strategy, as TPM was resource intensive and, although the model predicted that the resources would be justified, the healthcare system was not currently equipped to perform a large number of such procedures, mostly under general anaesthetic, resulting in an unrealistic burden for histopathology services. Thus, the model generated results with this strategy excluded and all prostate biopsies within the follow-up were TRUS,

Previous diagnostic tests		Optimal strategy	
MRI Likert score	**No. of negative biopsies**	**20k/QALY**	**30k/QALY**
1 or 2	0	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
1 or 2	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
1 or 2	2	3-yearly %free PSA; if ≤15% → mpMRI; if Likert ≥4 →TPM	2-yearly PSA; if velocity ≥0.75 ng/ml/year → mpMRI; if Likert ≥4 →TPM
3	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
3	2	2-yearly %free PSA; if ≤15% → mpMRI; if Likert ≥4 →TPM	2-yearly PSA; if velocity ≥0.75 ng/ml/year → mpMRI; if Likert ≥4 →TPM
4	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
4	2	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
5	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
5	2	2-yearly PSA; if density ≥0.15ng/ml/ml → TRUS	Immediate TPM for all; no subsequent follow-up
no MRI	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
no MRI	2	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up

Measures derived from PSA tests, including velocity at a threshold of 0.75 ng/ml/year and density at a threshold of 0.15 ng/ml/ml, appear to be reliable indicators that trigger further diagnostics within the majority of subpopulations. However, “no screening” strategy appears optimal for the lowest-risk subpopulation who had MRI Likert scores of 1 or 2 and 2 previous negative biopsies, unless QALYs are valued at a little over £20,000 each.The model generates consistent results, as the optimal frequency of tests changes proportionally with the potential risk of disease. For example, within the population who had negative mpMRI (Likert 1 or 2), the optimal frequency of the PSA velocity test was every 6 months, every year or 2-yearly for people who had no biopsy, 1 biopsy or 2 biopsies, respectively (when QALYs are valued at £30,000). The percentage of free PSA test appears effective in directing people to further diagnostics. The strategy, where people receive this test every 6 months and, if the percentage of free PSA was ≤15%, , they were directed to TRUS, seems to be optimal within the population who had MRI Likert score of 5 and 1 previous negative biopsy.

Table 4.

Table 3: Optimal follow-up strategies for different sub-populations, including the strategy where all patients are eligible to receive TPM

Previous diagnostic tests		Optimal strategy	
MRI Likert score	**No. of negative biopsies**	**20k/QALY**	**30k/QALY**
1 or 2	0	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
1 or 2	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
1 or 2	2	3-yearly %free PSA; if ≤15% → mpMRI; if Likert ≥4 →TPM	2-yearly PSA; if velocity ≥0.75 ng/ml/year → mpMRI; if Likert ≥4 →TPM
3	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
3	2	2-yearly %free PSA; if ≤15% → mpMRI; if Likert ≥4 →TPM	2-yearly PSA; if velocity ≥0.75 ng/ml/year → mpMRI; if Likert ≥4 →TPM
4	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
4	2	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
5	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
5	2	2-yearly PSA; if density ≥0.15ng/ml/ml → TRUS	Immediate TPM for all; no subsequent follow-up
no MRI	1	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up
no MRI	2	Immediate TPM for all; no subsequent follow-up	Immediate TPM for all; no subsequent follow-up

Measures derived from PSA tests, including velocity at a threshold of 0.75 ng/ml/year and density at a threshold of 0.15 ng/ml/ml, appear to be reliable indicators that trigger further diagnostics within the majority of subpopulations. However, “no screening” strategy appears optimal for the lowest-risk subpopulation who had MRI Likert scores of 1 or 2 and 2 previous negative biopsies, unless QALYs are valued at a little over £20,000 each.The model generates consistent results, as the optimal frequency of tests changes proportionally with the potential risk of disease. For example, within the population who had negative mpMRI (Likert 1 or 2), the optimal frequency of the PSA velocity test was every 6 months, every year or 2-yearly for people who had no biopsy, 1 biopsy or 2 biopsies, respectively (when QALYs are valued at £30,000). The percentage of free PSA test appears effective in directing people to further diagnostics. The strategy, where people receive this test every 6 months and, if the percentage of free PSA was ≤15%, , they were directed to TRUS, seems to be optimal within the population who had MRI Likert score of 5 and 1 previous negative biopsy.

Table 4: Optimal follow-up strategies for different sub-populations, excluding TPM as part of any strategy

Previous diagnostic tests		Optimal strategy	
MRI Likert score	**No. of negative biopsies**	**20k/QALY**	**30k/QALY**
1 or 2	0	Immediate TRUS for all; no subsequent follow-up	6-monthly PSA; if velocity ≥0.75 ng/ml/year → TRUS
1 or 2	1	Immediate TRUS for all; no subsequent follow-up	1-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS
1 or 2	2	no screening	2-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS
3	1	2-yearly PSA; if density ≥0.15ng/ml/ml → TRUS	1-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS
3	2	2-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS	1-yearly PSA; if velocity ≥0.75 ng/ml/year →TRUS
4	1	1-yearly PSA; if density ≥0.15ng/ml/ml → TRUS	6-monthly PSA; if velocity ≥0.75 ng/ml/year → TRUS
4	2	2-yearly PSA; if density ≥0.15ng/ml/ml →TRUS	1-yearly PSA; if density ≥0.15 ng/ml/ml → TRUS
5	1	6-monthly %free PSA; if ≤15% →TRUS	6-monthly PSA; if velocity ≥0.75 ng/ml/year → TRUS
5	2	2-yearly PSA; if density ≥0.15 ng/ml/ml → TRUS	1-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS
no MRI	1	1-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS	6-monthly PSA; if velocity ≥0.75 ng/ml/year →TRUS
no MRI	2	2-yearly PSA; if velocity ≥0.75 ng/ml/year → mpMRI; if Likert ≥4 → TRUS	1-yearly PSA; if velocity ≥0.75 ng/ml/year → TRUS

Sensitivity analysis

Our findings seemed to be robust, in terms of the types of screening tests triggering further investigation, in a number of different scenarios. However, when the modelled cohort entered the model at a younger age (52 years), strategies with greater frequency were found to be optimal. For example, the strategy associated with the highest net health benefits for people that had Likert score at 3 and previous negative biopsy included PSA velocity at a threshold of 0.75 ng/ml/year determining people who need TRUS, but to be performed annually instead of every 2 years in the base case analysis. In addition, “no screening” strategy was not found optimal anymore in any sub-population.

Following the strategy where all receive an immediate TPM inevitably leads to overtreatment of people with clinically non-significant disease, which may cause harm more than benefits, e.g. increased anxiety as a consequence of the diagnosis. In the absence of evidence on this disutility due to overdiagnosis, we did not include it in the base-case analysis. However, to explore its potential impact, we applied disutility (0.05) to the diagnosis of low-risk prostate cancer in a scenario analysis. This resulted in the “no screening” strategies being more encouraged within the least risk sub-population. This scenario was also in favour of less frequent screening test, using PSA velocity at a threshold of 0.75 ng/ml/year, PSA density at threshold of 0.15 ng/ml/ml and %free PSA.

In a further scenario analysis, we applied both the disutility associated with the diagnosis of clinically non-significant disease and a higher cost of TPM, assuming that it required staying overnight in hospital in all cases. Under these conditions, the strategy of offering an immediate TPM to all would not be optimal in the majority of subpopulations. Optimal

strategies included PSA screening tests, using PSA velocity at a threshold of 0.75 ng/ml/year, PSA density at threshold of 0.15 ng/ml/ml and %free PSA. The frequency of test varied based on the risk from yearly to 3-yearly based on the prostate cancer risk. For people with negative biopsies but did not receive Mp-MRI, optimal strategies included Mp-MRI to direct people to prostate biopsy, if Likert score ≥4.

Evidence statements

Clinical Evidence statements

Prostate cancer antigen 3 urinary assay (PCA3)

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios*:
    - A PCA3 cut-off of ≥20 **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (very low-quality evidence from 10 cross sectional studies comprising 2,235 participants; 95% confidence intervals range within slight increase)
    - A PCA3 cut off of ≥35 **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (very low-quality evidence from 13 cross sectional studies comprising 3,828 participants; 95% confidence intervals range within slight increase)
    - A PCA3 cut-off of ≥50 leads to a **moderate increase** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (very low-quality evidence from 10 cross-sectional studies comprising 1,806 participants; 95% confidence intervals ranges from slight increase to moderate increase)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios)*
    - A PCA3 cut-off of <20 leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (very low-quality evidence from 10 cross-sectional studies comprising 2,235 participants; 95% confidence intervals range from moderate decrease to moderate decrease).
    - A PCA3 cut off of <35 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (very low-quality evidence from 13 cross-sectional studies comprising 3,828 participants; 95% confidence intervals range from slight decrease to moderate decrease).
    - A PCA3 cut-off of <50 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (very low-quality evidence from 10 cross-sectional studies comprising 1,806 participants; 95% confidence intervals ranges from slight increase to moderate decrease)

Multiparametric MRI

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios*:
    - A Likert or PIRAD score ≥3 **does not alter** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer defined as either any cancer or clinically significant (high quality evidence from 4 cross-sectional studies comprising 967 participants; 95% confidence intervals range from slight increase to slight increase)

  - A PIRADs score ≥4 leads to a **moderate increase** in the probabitity that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (low-quality evidence from 2 cross-sectional studies comprising 538 participants, 95% confidence intervals range from moderate increase to moderate increase)
  - A PIRADs score of 5 leads to a **very large increase** in the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (high-quality evidence from 1 cross-sectional study comprising 249 participants, 95% confidence intervals ranged from large increase to very large increase)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios)*
  - A Likert or PIRAD score <3 leads to a **large decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (high quality evidence from 4 cross-sectional studies comprising 738 participants; 95% confidence intervals range from moderate decrease to large decrease)
  - A PIRADSs score <4 leads to a **large decrease** in the probabitity that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (low quality evidence from 2 cross-sectional studies comprising 538 participants, 95% confidence intervals range from moderate decrease to very large decrease)
  - A PIRADs score <5 leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (high quality evidence from 1 cross-sectional study comprising 249 participants, 95% confidence intervals ranged from slight decrease to moderate decrease)

Total prostate specific antigen (PSA)

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
  - A PSA ≥4ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 1,112 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥5ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate-quality evidence from 4 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥6ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Very low-quality evidence from 4 cross-sectional studies comprising 509 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥7ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate-quality evidence from 3 cross-sectional studies comprising 299 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥8.5ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional studies

comprising 355 participants; 95% confidence intervals range from slight decrease to slight increase)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A PSA ≥4ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 1,112 participants; 95% confidence intervals range from moderate decrease to moderate increase)
    - A PSA ≥5ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from large decrease to slight increase)
    - A PSA ≥6ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 4 cross-sectional studies comprising 509 participants; 95% confidence intervals range from slight decrease to moderate decrease)
    - A PSA ≥7ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 299 participants; 95% confidence intervals range from slight decrease to slight increase)
    - A PSA ≥8.5ng/ml **could not differentiate** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional studies comprising 355 participants; 95% confidence intervals range from large decrease to slight increase)

Prostate Specific Antigen density

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A PSA ≥0.09ng/ml/ml **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 2 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight increase to slight increase)
    - A PSA density ≥0.10ng/ml/ml **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 2 cross-sectional studies comprising 1,066 participants; 95% confidence intervals range from slight increase to slight increase)
    - A PSA density ≥0.15ng/ml/ml **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 7 cross-sectional studies comprising 1,319 participants; 95% confidence intervals range from slight increase to slight increase)
    - A PSA density ≥0.30ng/ml/ml leads to a **moderate increase** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 267 participants; 95% confidence intervals range from slight increase to moderate increase)
    - A PSA density ≥0.38ng/ml/ml **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 1 cross-sectional studies comprising

67 participants; 95% confidence intervals range from slight increase to moderate increase)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A PSA density <0.09ng/ml/ml leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low-quality evidence from 2 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight decrease to large decrease)
    - A PSA density <0.10ng/ml/ml leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Low-quality evidence from 3 cross-sectional studies comprising 1,066 participants; 95% confidence intervals range from slight decrease to moderate decrease)
    - A PSA density <0.15ng/ml/ml **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 7 cross-sectional studies comprising 1,319 participants; 95% confidence intervals range from moderate decrease to slight decrease)
    - A PSA density <0.30ng/ml/ml leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low-quality evidence from 3 cross-sectional studies comprising 267 participants; 95% confidence intervals range from slight decrease to moderate decrease)
    - A PSA density <0.38ng/ml/ml leads to a **moderate decrease** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 1 cross-sectional studies comprising 67 participants; 95% confidence intervals range from slight decrease to very large decrease)

Prostate Specific Antigen velocity

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A PSA velocity ≥1.19ng/ml/year **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (moderate-quality evidence from 1 cross-sectional studies comprising 127 participants; 95% confidence intervals range from slight increase to slight increase)
    - A PSA velocity ≥0.75ng/ml/year **does not alter** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (low-quality evidence from 7 cross-sectional studies comprising 1,364 participants; 95% confidence intervals range from slight decrease to slight increase)
    - A PSA velocity ≥0.28ng/ml/year **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (moderate-quality evidence from 1 cross-sectional studies comprising 127 participants; 95% confidence intervals range from slight decrease to slight increase)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A PSA velocity cutoff of <1.19ng/ml/year **could not differentiate** the probability that a person persistently suspected of prostate cancer after an intial negative biopsy has prostate cancer (Low-quality evidence from 1 cross-sectional study

comprising 127 participants; 95% confidence intervals range from slight decrease to very large decrease)
    - A PSA velocity <0.75ng/ml/year **does not alter** the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (low-quality evidence from 7 cross-sectional studies comprising 1,364 participants; 95% confidence intervals range from slight decrease to slight increase)
    - A PSA velocity cutoff of <0.28ng/ml/year **could not differentiate** the probability that a person persistently suspected of prostate cancer after an intial negative biopsy has prostate cancer (Low-quality evidence from 1 cross-sectional study comprising 127 participants; 95% confidence intervals range from slight decrease to very large decrease

Prostate Specific Antigen density of the transition zone (PSA-TZD)

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A PSA-TZD ≥0.20ng/ml/ml **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 2 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight increase to slight increase)
    - A PSA-TZD ≥0.25ng/ml/ml **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 2 cross-sectional studies comprising 978 participants; 95% confidence intervals range from slight increase to slight increase)
- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A PSA-TZD <0.20ng/ml/ml leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (moderate-quality evidence from 2 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight decrease to moderate decrease)
    - A PSA-TZD <0.25ng/ml/ml leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (moderate-quality evidence from 1 cross-sectional studies comprising 978 participants; 95% confidence intervals range from slight decrease to moderate decrease)

Prostate Health Index (PHI)

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A PHI score ≥25 **has no diagnostic value** in the diagnosis of prostate cancer after a negative intial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 95 participants; 95% confidence intervals range from slight decrease to slight increase)
    - A PHI score ≥30 **does not alter** the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 222 participants; 95% confidence intervals range from slight increase to slight increase)
    - A PHI score ≥35 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Very low -quality evidence from 1 cross-sectional studies

comprising 95 participants; 95% confidence intervals range from slight increase to a moderate increase)
    - A PHI score ≥40 **does not meanignfully alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low -quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight increase to moderate increase)
    - A PHI score cut off of ≥48.9 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional studies comprising 170 participants; 95% confidence intervals range from slight increase to moderate increase)
    - A PHI score cut off of ≥62 leads to a **moderate increase** in the probability (Moderate-quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight increase to large increase)
- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A PHI score cut off of <25 **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 95 participants; 95% confidence intervals range from large decrease to moderate increase)
    - A PHI score cut off of <30 leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight decrease to large decrease)
    - A PHI score cut off of <35 leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 95 participants; 95% confidence intervals range from large decrease to a slight increase)
    - A PHI score cut off of <40 leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight decrease to moderate increase)
    - A PHI score cut off of <48.5 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional study comprising 170 participants; 95% confidence intervals range from slight decrease to moderate decrease)
    - A PHI score cut off of <62 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 222 participants; 95% confidence intervals range from slight decrease to slight decrease)

Prostate Health Index (PHI) in MRI negative population

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:

  - A PHI score ≥25 **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative intial mpMRI has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 94 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PHI score ≥30 **does not alter** the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 94 participants; 95% confidence intervals range from slight increase to slight increase)
  - A PHI score ≥35 **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Very low -quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from slight increase to a moderate increase)
  - A PHI score ≥40 leads to a **moderate increase** in the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Very low -quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from slight increase to moderate increase)
- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
  - A PHI score cut off of <25 **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from very large decrease to moderate increase)
  - A PHI score cut off of <30 leads to a **large decrease** in the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from slight decrease to very large decrease)
  - A PHI score cut off of <35 leads to a **large decrease** in the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from moderate decrease to very large decrease)
  - A PHI score cut off of <40 leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from slight decrease to moderate decrease)

Percentage Free Prostate Specific Antigen (%fPSA)

Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios):

  - A %fPSA ≥ 10% **could not differentiate** the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Very low-quality evidence from 4 cross-sectional studies comprising 481 participants; 95% confidence intervals range from slight decrease to large increase)
  - A %fPSA ≥ 15% **does not meaningfully alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 7 cross-sectional studies comprising

1,253 participants; 95% confidence intervals range from slight increase to moderate increase)
    - A %fPSA ≥ 20% **does not alter** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low -quality evidence from 4 cross-sectional studies comprising 720 participants; 95% confidence intervals range from slight increase to slight increase)
    - A %fPSA ≥ 25% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 3 cross-sectional studies comprising 1,038 participants; 95% confidence intervals range from slight increase to slight increase)
    - A %fPSA ≥ 30% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 5 cross-sectional studies comprising 1,290 participants; 95% confidence intervals range from slight increase to slight increase)
    - A %fPSA ≥ 35% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 1 cross-sectional studies comprising 820 participants; 95% confidence intervals range from slight increase to slight increase)
    - A %fPSA ≥ 38% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 1 cross-sectional studies comprising 820 participants; 95% confidence intervals range from slight increase to slight increase)
- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A %fPSA <10% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 481 participants; 95% confidence intervals range from slight decrease to slight decrease)
    - A %fPSA < 15% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low-quality evidence from 7 cross-sectional studies comprising 1,253 participants; 95% confidence intervals range from slight decrease to slight decrease)
    - A %fPSA < 20% **does not alter** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 4 cross-sectional studies comprising 720 participants; 95% confidence intervals range from slight decrease to slight decrease)
    - A %fPSA <25% leads to a **moderate decrease** in the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Very low-quality evidence from 6 cross-sectional studies comprising 1,038 participants; 95% confidence intervals range from slight decrease to moderate decrease)
    - A %fPSA <30% **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low-quality evidence from 5 cross-sectional studies comprising 1,290 participants; 95% confidence intervals range from slight decrease to slight decrease)
    - A %fPSA <35% leads to a **large decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 820 participants; 95% confidence intervals range from moderate decrease to a very large decrease)
    - A %fPSA <38% leads to a **large decrease** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 1 cross-sectional studies comprising 820

participants; 95% confidence intervals range from moderate decrease to a very large decrease)

PSA doubling time

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A PSA doubling time of 24, 30, 50 and 70 months **has no diagnostic value** in the diagnosis of prostate cancer in a person persistently suspected of the disease (Moderate – Low quality evidence from 1 crosssectional study)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A PSA doubling time of 24, 30, 50 and 70 months **has no diagnostic value** in the diagnosis of prostate cancer in a person persistently suspected of the disease (Moderate – Low quality evidence from 1 crosssectional study)

Digital rectal examinations

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A positive digital rectal examination leads to a **moderate increase** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 5 cross-sectional studies comprising 641 participants; 95% confidence intervals range from slight increase to moderate increase)
- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
    - A negative digital recatal examination **does not alter** the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 4 cross-sectional studies comprising 576 participants; 95% confidence intervals range from slight decrease to slight decrease)

Economic evidence statements

TPM included in the analysis

One directly applicable original cost–utility model with potentially serious limitations showed that the optimal strategy for the majority of subpopulations is for all candidates to receive an immediate TPM and no subsequent follow-up.

TPM excluded from the analysis

One directly applicable original cost–utility model with potentially serious limitations showed that the 'no screening' strategy, where people are directed to prostate biopsy only if they develop symptoms, appears to be optimal for people with Likert <3 and 2 previous negative biopsies at a cost-effectiveness threshold of £20k/QALY. For people with Likert score <3 and no or 1, previous biopsy, a strategy where all candidates receive TRUS and no subsequent follow-up, seems to be optimal. The strategies including PSA velocity at a threshold of 0.75 ng/ml/year, PSA density at a threshold of 0.15 ng/ml/ml or %free PSA at a threshold of 15% that determined people who need prostate biopsy appear optimal for the majority of subpopulations. The frequency of screening tests varies based on the disease risk between 6-monthly, yearly or 2-yearly. The frequency of every 2 years seemed to be optimal for people with Likert score 3 and previous negative biopsies (either 1 or 2) and also for people with Likert 4 and Likert 5 and two previous negative biopsies. For people with Likert 4 and

Likert 5 and 1 previous negative biopsy, the optimal frequency was every year and every six months, respectively.

For people with 1 or 2 previous negative biopsies and no previous mpMRI, the strategies of a yearly screening test followed by TRUS or 2-yearly screening test followed by mpMRI with a cutoff of Likert score ≥4 appear optimal, respectively. Raising the cost-effectiveness threshold from £20,000/QALY to £30,000/QALY allows strategies with greater frequency, e.g. every year instead of 2-yearly, to be optimal.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcome was whether or not the index tests could increase the probability of identifying or excluding clinically significant prostate cancer in people who had at least one negative initial biopsy, expressed as likelihood ratios.

The quality of the evidence

Clinical effectiveness

Prior to gathering evidence for this review question, the committee explained that it was very difficult to find any published literature which would directly answer the review question. As a result, it chose this question as a priority for health economics modelling. It decided to identify studies reporting accuracy data for PSA measures that can help simulate strategies to follow-up people who have a raised PSA, negative MRI and/ or negative biopsy.

Thirty-eight studies were included in this review. The majority of the studies were at either moderate or high risk bias owing to poor patient selection strategies and not choosing index tests thresholds a priori. The studies providing evidence for multiparametric MRI (Boesen 2018, Lista 2015, Simmons 2017 and Tsivian 2016) had low to moderate risk of bias owing to meeting most of the elements of a good diagnostic cross-sectional study as assessed using the QUADAS tool. Only one of these studies was from the UK (Simmons (2017)). All the studies used a PIRADS scoring system. The committee explained that it would prefer to use Likert scoring as this takes into account clinical factors and not just the image, however, it did not disregard the presented evidence.

Most of the studies provided evidence for a number of index tests. All the primary studies were directly applicable and used transrectal ultrasound biopsy as the reference standard. The majority of the included studies did not distinguish the type of prostate cancer (significant or non significant cancer).

All study partiticipants had never had mpMRI but had previously had at least one negative biopsy, apart from those from the study by Gnanapragasam (2016) who had both a negative biopsy and a negative mpMRI.

Benefits and harms

The committee reviewed evidence on the diagnostic accuracy of prostate cancer antigen 3 urinary assay (PCA3) from 17 studies (listed in GRADE tables Prostate cancer antigen 3 urinary assay). Its consideration of this evidence will update NICE's existing guidance on PCA3 assay and the prostate health index (DG17). PCA3 was investigated at 3 thresholds – 20, 35 and 50. At all three thresholds, the evidence showed that PCA3 was not a useful index test to help identify prostate cancer in people with at least one negative TRUS biopsy. Because the committee saw no evidence that either technique represents an effective use of

NHS resources in the follow up of people who have had a negative TRUS biopsy, the committee stated that it do not recommend the use of PCA3 assay in this population group.

The committee reviewed evidence on the diagnostic accuracy of mpMRI from 4 cross-sectional studies (Boesen 2018, Lista 2015, Simmons 2017 and Tsivian 2016). These studies provided evidence at three thresholds – MRI PIRADS score ≥3, ≥4 and 5. The committee was not surprised by the ability of mpMRI to identify lesions as this was consistent with the evidence presented for the biopsy naïve population. All four studies regarded an MRI PIRADS score of 1 or 2 as 'negative' MRI. As explained in the evidence for the biopsy naïve population – the committee prefer the use of Likert scoring system as it takes into consideration the other clinical factors presented by the patients, unlike PIRADS scoring system that only consider the lesions. Based on the evidence that an MRI score of 1 or 2 represents negative biopsy, the committee made recommendations that define Likert 1 or 2 as negative MRI.

The committee reviewed evidence on the diagnostic accuracy of total prostate specific antigen (PSA) from up to 7 cross-sectional studies (listed in GRADE tables Total prostate specific antigen). PSA was investigated at 5 thresholds – 4, 5, 6, 7 and 8.5ng/ml. At all 5 thresholds, the evidence showed that PSA was not a useful index test to help identify prostate cancer in people with with at least one negative TRUS biopsy. As a result, the committee did not make any recommendation regarding the use of PSA in the follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy

The committee reviewed evidence on the diagnostic accuracy of prostate specific antigen density from up to 8 cross-sectional studies listed in GRADE tables Prostate specific antigen density. PSAD was investigated at 5 thresholds – 0.09, 0.10, 0.15. 0.30 and 0.38ng/ml/ml. Evidence showed that the most useful threshold was 0.30ng/ml/ml. This evidence was provided by 2 Japanese cross-sectional studies (Okegawa (2003) and Ohigashi (2005)). The committee had reservations about the applicability of this evidence because the study was conducted in a Japanese setting.The committee explained that a threshold of 0.30ng/ml/ml was too high to be a useful marker in a clinical setting, because at that threshold some abnormality is expected, and therefore the committeeand was not surprised by the good specificity at that threshold. Based on positive and negative likelihood ratio, the evidence showed that a threshold of 0.30ng/ml/ml leads to a moderate increase and moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer. The committee had reservations on the fact that the two studies were conducted in Japanese settings and may not be applicable to the UK population. The majority of the studies provided evidence for a threshold of 0.15ng/ml/ml. The committee noted that this threshold was more acceptable for a UK population because that is a threshold used in clinical practice. In terms of positive and negative likelihood ratio, the evidence showed that a PSAD threshold of 0.15ng/ml/ml does not alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer. However, the committee explained that the accuracy performance at a threshold of 0.15ng/ml/ml was acceptable. As a result, the committee recommended that a PSAD of 0.15ng/ml/ml should be used to decide next steps (prostate biopsy or discharge) for people with raised PSA, MRI Likert 1 or 2 and/or a negative biopsy.

The committee also reviewed evidence on the diagnostic accuracy of prostate specific antigen velocity (PSAV) from up to 7 cross-sectional studies listed in GRADE tables Prostate specific antigen velocity. PSAV was investigated at 3 thresholds – 1.19, 0.75, 0.28ng/ml/year. In terms of positive and negative likelihood ratio, the evidence showed that a PSAV threshold of 0.75ng/ml/year could not alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer. However, the committee explained that the accuracy performance at a threshold of 0.75ng/ml/year was acceptable. As a result, the committee recommended that a PSAV of 0.75ng/ml/year should be used to decide next steps (prostate biopsy or discharge) for people with raised PSA, MRI Likert 1 or 2 and/or a negative biopsy.

The committee reviewed evidence on the diagnostic accuracy of percent free prostate specific antigen (%fPSA) from up to 7 cross-sectional studies (listed in GRADE tables Percent free prostate specific antigen). %fPSA was investigated at 6 thresholds – 10%, 15%, 20%, 25%, 30% and 35%. At all 6 thresholds, the evidence showed that %fPSA was not a useful index test to help identify prostate cancer in people with with at least one negative TRUS biopsy. As a result, the committee did not make any recommendations regarding the use of %fPSA in the follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy.

The committee reviewed evidence on the diagnostic accuracy of digital rectal examination (DRE) from up to 6 cross-sectional studies (listed in GRADE tables Digital Rectal Examination). The evidence showed that DRE was not a useful index test to help identify prostate cancer in people with with at least one negative TRUS biopsy. As a result, the committee did not make any recommendations regarding the use of DRE in the follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy.

The committee reviewed evidence on the diagnostic accuracy of prostate health index (PHI) from 4 studies (Scattoni (2003), Lazzeri (2012), Porpiglia (2014) and Gnanapragasam (2016)). Its consideration of this evidence updates NICE's existing guidance on PCA3 assay and the prostate health index (DG17). None of the evidence could be meta-analysed as the studies used different thresholds. The thresholds were 25, 30, 35, 40, 48.8 and 62. The evidence showed that PHI was good at identifying negative features in people with prostate cancer compared to those without, however it was not useful at identifying positive features in people with prostate cancer compare to those without. In addition, the test was not cost effective within the normal cost thresholds. Due to this, the committee concluded PHI is not a useful index test to help identify prostate cancer in people with with at least one negative TRUS biopsy and MRI negative. As a result, the committee stated that they do not recommend the use of PHI in the follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy.

Cost effectiveness and resource use.

The committee reviewed the economic evidence provided by the original economic model . They agreed that the analysis addressed the decision problem, in terms of the input parameters, structure, assumptions and the follow-up strategies simulated. However, they noted some limitations – in particular, the derivation of the sensitivity of repeat TRUS biopsy in people with a previous negative biopsy. They noted that the source used to derive the relation between the sensitivity of initial and subsequent TRUSs reflected practice from 20 years ago, when such procedures were performed somewhat differently (in particular, fewer cores were taken). However, they noted that these data were only used to estimate the relative sensitivity of first and subsequent biopsies, which is then applied to a more reliable baseline (from a large, recent UK study, PROMIS), and agreed that, in the absence of contemporary, high-quality evidence, this approach was acceptable.

The committee also noted that the strategy that seemed to be optimal for the majority of modelled subpopulations, where all receive an immediate TPM, would be associated with overdiagnosis, which means people with clinically non-significant disease would be identified causing them anxiety and probably exposing them to treatments that are not likely to provide any extended survival. They noted that this type of biopsy was far more resource consuming and considerably affected people's quality of life compared with TRUS. The model explored the impact of associating disutility with the diagnosis of people with clinically non-significant disease in a sensitivity analysis. In this scenario, the strategy where all candidates receive an immediate TPM was found not to be optimal in a number of sub-population. The committee agreed that the analysis excluding TPM would be more informative to make their recommendations.

The committee agreed that the approach of addressing 11 subpopulations, based on Likert score (1 to 5) obtained from previous mpMRI and/or up to 2 previous negative biopsies was sensible, as this reflected the potential population introduced by the recommendations made based on evidence review D. The committee agreed that the intensity of follow-up strategies should correspond to the intensity of diagnostic tests people underwent initially i.e. negative findings on mpMRI and/or 1 or 2 negative biopsies. The more diagnostic tests people received as initial diagnosis , the less frequent follow-up strategies were required. The committee agreed that the economic model generated consistent results in this context.

The committee noted that a follow-up strategy could be optimal for a number of subpopulations, but with more intensive frequency for higher risk populations. It also agreed that strategies with PSA-based screening tests, including PSA density at a threshold of 0.15 ng/ml/ml, PSA velocity at a threshold of 0.75 ng/ml/year and % free PSA, appeared to be within the optimal strategies, were clinically meaningful in terms of thresholds. However, the committee noted that the % free PSA test required more sophisticated procedures than other PSA measurements, which may affect the uptake of this test in primary care settings. They noted that the accuracy performance of PSA density and velocity tests at the mentioned thresholds was sufficiently reliable compared to % free PSA test. They also noted that, if PSA kinetics were to be used, an absolute measure (PSA velocity) performed much better than a relative one (PSA doubling time).
The committee agreed that the model's findings were sufficient to make recommendations about following up people with Likert score 1 or 2 and no previous biopsy by offering 6-monthly and then yearly PSA test, with repeat biopsy indicated if density ≥0.15 ng/ml/ml or velocity ≥0.75 ng/ml/year. The same strategy was recommended to people with Likert 1 or 2 and at least 1 previous negative biopsy but, as the probability of undiagnosed disease is lower in such people, the optimal follow-up frequency may be extended to every 2 years.

Appendices

Appendix A – Review protocols

Review protocol: What is the most clinically- and cost-effective follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy?

ID	Field (based on PRISMA-P	Content
I	Review question	What is the most clinically- and cost-effective follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy?
II	Type of review question	Diagnostic
III	Objective of the review	To identify studies reporting accuracy data for PSA measures that can help simulate strategies to follow-up people who have a raised PSA, negative MRI and/ or negative biopsy. No existing recommendations
IV	Eligibility criteria – population/disease/condition/issue/ domain	• People who have a raised PSA and negative MRI • People who have a raised PSA and negative biopsy
V	Index Tests	• Individual or repeated PSA tests and calculations derived from them (including tPSA, fPSA, %fPSA, PSAD) • Digital rectal examination

		• MRI
VI	Reference (gold) standard	• Biopsy (TRUS or TPM) • Radical prostatectomy specimen • Clinical emergence of cancer (follow up at least 10 years)
VII	Outcomes and prioritisation	Diagnostic accuracy • Sensitivity and specificity • Likelihood ratios
VIII	Eligibility criteria – study design	• Diagnostic cross-sectional studies • Systematic reviews of diagnostic cross-sectional studies
IX	Other inclusion exclusion criteria	• Non-English language papers • Reviews • Unable to calculate 2x2 tables
X	Proposed sensitivity/sub-group analysis, or meta-regression	• Negative MRI • Negative biopsy • Repeat biopsy • Biopsy naive
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.

XII	Data management (software)	See appendix B below – section 1.3
XIII	Information sources – databases and dates	See appendix C of relevant chapter. No date limits will be used.
XIV	Identify if an update	This is a new clinical area, no previous question in previous updates. Committee agreed to no date limits for this question. **Original question**: New question, no original question in guideline/. **Recommendations that may be affected:** No existing recommendations.
XV	Author contacts	Guideline updates team, National Institute for Health and Care Excellence (contact adam.okeefe@nice.org.uk)
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables).

XX	Methods for assessing bias at outcome/study level	See Appendix B below – see section 1.4.1
XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B below
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B below – see section 1.4.2
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B below – see section 1.4.3 and 1.4.5
XXIV	Assessment of confidence in cumulative evidence	See Appendix B below - see section 1.4.3
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the guideline update. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE will undertake systematic literature searches, appraise the evidence, conduct meta-analyses and cost-effectiveness analyses where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.

XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B – Methods

Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 5: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Evidence statements

The evidence statements were based on likelihood ratios (a MID for positive likelihoods ratio was set at 2, and a corresponding MID for negative likelihood ratios at 0.5) and these are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the index test lead to a moderate, large and very large increase/decrease in probability of disease
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the index test could not meaningfully alter the probability of disease.
- In all other cases, we state that the index test could not alter the probability between the comparators
- When the likelihood ratios were reversed for example – positive likelihood ratio of 0.1 and negative likelihood ratio of 3, we state that the index test has no diagnostic value.

Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the `mada` package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

To meta-analyse the data, - in any cases where different thresholds were used across studies the following rules were adapted

Total prostate specific antigen

- Thresholds were pooled if they were within a point of each other or within five points depending on the sensitivity of the data
- If the same study provided studies within the same range, the value closest to the middle of the range was used
- If there was only one study within a range then the actual study threshold was stated – rather than the threshold range.

Prostate cancer antigen 3 urinary assay

- Thresholds were pooled using the following ranges, these were adapted from some of the included articles that defined the cutoff points in a similar way -:
    - cutoff of 20 – any values between 0-20
    - cutoff of 35 any values between 21-35
    - cut off 50 any values between 36-50

- If the same study provided studies within the same range, the value closest to the top of the range was used

Percent free Prostate specific antigen

- Thresholds were pooled within five points so that a threshhold of <10% includes values from 5-9%
- If the same study provided studies within the same range, the value closest to the middle of the range was used
- If there was only one study within a range then the actual study threshold was stated – rather than the threshold range.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 6 below.

Table 6: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.

GRADE criteria	Reasons for downgrading quality
	Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for a positive likelihood ratio spanned 2, the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratios that spanned 0.5 led to downgrading for serious imprecision. Any likelihood ratios that spanned both 0.5 and 2 were downgraded twice, as suffering from very serious imprecision. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Appendix C – Literature search strategies

Search summary

The search strategies were based on the review protocol provided. The prostate cancer population terms have been removed for this question as the main focus was for patients who haven't yet been diagnosed with prostate cancer.

Clinical searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- Epub Ahead of Print (Ovid)

The clinical searches were conducted in April 2018.

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
1 Prostate-Specific Antigen/ 2 (Prostate* specific antigen adj2 (rais* or high* or elevate* or rise* or increase*)).tw. 3 (PSA adj2 (rais* or high* or elevate* or rise* or increase*)).tw. 4 (Kallikrein or semenogelase or seminin or gamma seminoprotein or gamma-seminoprotein or HK3).tw. 5 Prostate Health Index.tw. 6 PHI.tw. 7 or/1-6 8 *Magnetic Resonance Imaging/ 9 (magnet* adj2 (resonance* or imag* or scan* or spectroscop*)).tw. 10 (MR adj2 (resonance* or imag* or scan* or spectroscop*)).tw. 11 (Dynamic contrast* enhanc* adj2 (MR* or magnet*)).tw. 12 (contrast* adj2 (imag* or scan*)).tw. 13 ((MRI or MRSI or MP-MR* or MPMR*) adj4 prostat*).tw. 14 turbo spin echo*.tw. 15 ((diffusion* or weight*) adj2 imag*).tw. 16 ((DWI or DCE-MRI or T2W or TSE or T2-weighted MRI*) adj4 prostat*).tw. 17 (Multi-parametric or multiparametric* or biparametric* or bi-parametric*).tw. 18 or/8-17 19 *biopsy/ or *image-guided biopsy/

20 ((transrectal* or trans-rectal* or transperineal* or trans-perineal*) adj2 (ultrasound* or biops*)).tw.
21 ((saturat* or extend* or templat* or negative*) adj2 (ultrasound* or biops*)).tw.
22 ((TRUS or TRUSB) adj4 prostat*).tw.
23 or/19-22
24 7 and 18
25 7 and 23
26 or/24-25

Study design filters and limit

The McMaster diagnosis filter plus the prostate diagnosis subhedings (OVID) were appended to the strategy above and are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Filters presented below.

McMaster Diagnosis studies
1. sensitiv:.mp. OR diagnos:.mp. OR di.fs.

Prostate Diagnosis subheadings (OVID)
1. Prostate/dg or Prostatic Neoplasms/dg

An English language limit was applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) were also excluded.

Health Economics search strategy

Economic evaluations and quality of life data.

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to the population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant evidence and can be seen below.

An English language limit was applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) were also excluded.

The economic searches were conducted in April 2018.

Health Economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

Quality of life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Search summary

The search strategies were based on the review protocol provided.

The prostate cancer population terms have been removed from this startgey as the focus of this questions is patients who haven't been diagnosed with prostate cancer. The population was as follows:

- People who have a raised PSA and negative MRI.
- People who have a raised PSA and negative biopsy.

Clinical searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)

The clinical searches were conducted in April 2018

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Strategy:

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1 Prostate-Specific Antigen/
2 (Prostate* specific antigen adj2 (rais* or high* or elevate* or rise* or increase*)).tw.
3 (PSA adj2 (rais* or high* or elevate* or rise* or increase*)).tw.
4 (Kallikrein or semenogelase or seminin or gamma seminoprotein or gamma-seminoprotein or HK3).tw.
5 Prostate Health Index.tw.
6 PHI.tw.
7 or/1-6
8 *Magnetic Resonance Imaging/
9 (magnet* adj2 (resonance* or imag* or scan* or spectroscop*)).tw.
10 (MR adj2 (resonance* or imag* or scan* or spectroscop*)).tw.
11 (Dynamic contrast* enhanc* adj2 (MR* or magnet*)).tw.
12 (contrast* adj2 (imag* or scan*)).tw.
13 ((MRI or MRSI or MP-MR* or MPMR*) adj4 prostat*).tw.
14 turbo spin echo*.tw.
15 ((diffusion* or weight*) adj2 imag*).tw.

16	((DWI or DCE-MRI or T2W or TSE or T2-weighted MRI*) adj4 prostat*).tw.
17	(Multi-parametric or multiparametric* or biparametric* or bi-parametric*).tw.
18	or/8-17
19	*biopsy/ or *image-guided biopsy/
20	((transrectal* or trans-rectal* or transperineal* or trans-perineal*) adj2 (ultrasound* or biops*)).tw.
21	((saturat* or extend* or templat* or negative*) adj2 (ultrasound* or biops*)).tw.
22	((TRUS or TRUSB) adj4 prostat*).tw.
23	or/19-22
24	7 and 18
25	7 and 23
26	or/24-25

Study design filters and limit

The MEDLINE McMaster Diagnosis filter was appended to the strategy above along with the diagnosis subheadings that were available in MEDLINE (Ovid) related to the prostate. This is presented below and was translated for use in the MEDLINE In-Process and Embase databases.

MEDLINE McMaster Diagnosis filter.	
1	(sensitiv: or diagnos:).mp. or di.fs.
2	Prostate/dg or Prostatic Neoplasms/dg
3	or/1-2

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health Economics search strategy

Economic evaluations and quality of life data.

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant evidence and can be seen below.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

The economic searches were conducted in April 2018.

Health Economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

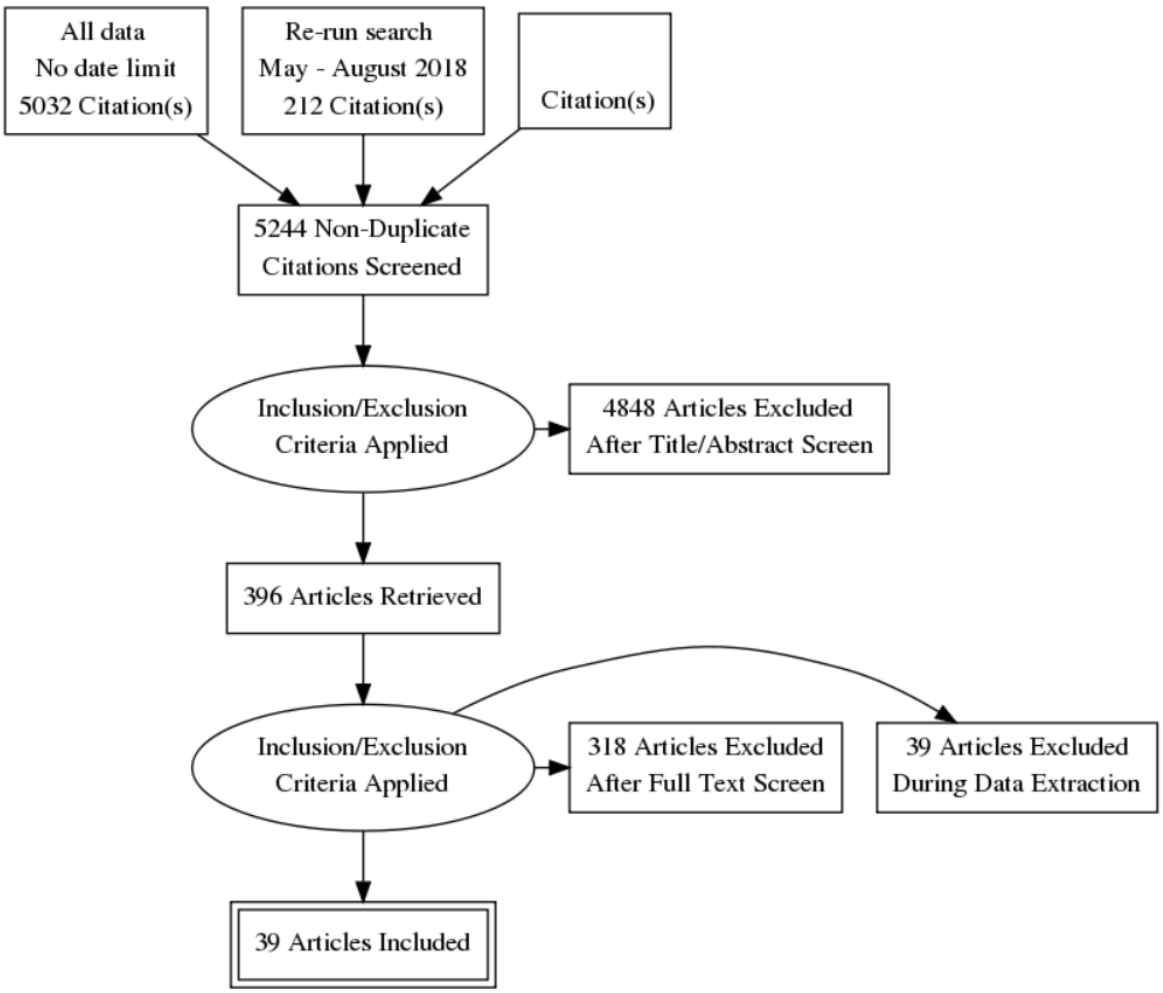
1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

Quality of life

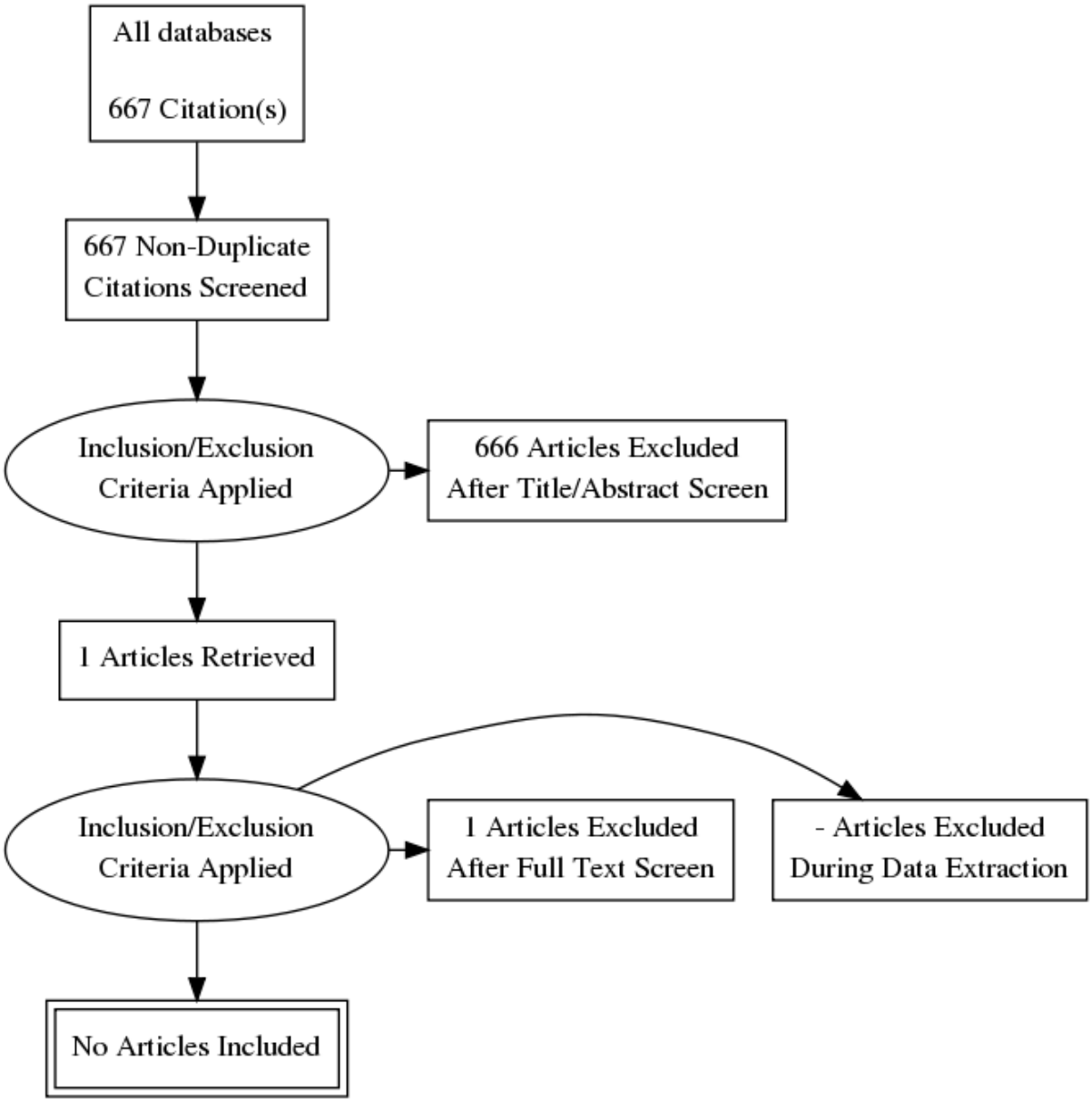
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix D – Study selection

Clinical evidence



Economic evidence



Appendix E – Clinical evidence tables

Short Title	Title	Study Characteristics	Quality Assurance
Abd-Alazeez (2014)	The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level--can it rule out clinically significant prostate cancer?	Study type Cross-sectional study Study details Study location UK Study dates not stated Sources of funding UK National Institute of Health Research Council, UCL Comprehensive Biomedical ResearchCentre London UK Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA Exclusion criteria Anyone who received less than 20 cores of template biopsy Sample characteristics Sample size 54 participants Median age (Range) 64 years (39-75)	Patient selection Unclear risk of bias Patient selection strategy was not provided Index test Low risk of bias Mp MRI was performed in a blined manner to the template biopsy as all imaging reports were committed to the electronic medical record before the biopsy result became available Reference standard Low risk of bias The reference standard matched the protocol and was regarded as the gold standard. It is unclear if the template biopsy was carried out in a blinded manner Flow and timing Unclear risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Moderate Moderate – as a result of the uncertainties surrounding

Short Title	Title	Study Characteristics	Quality Assurance
		PSA ng/ml median, range - 10 (2-23) Number of previous biopsies Between 1 and 3 biopsies Median Prostate volume 53 (19-136) Index test(s) mp-MRI MRI comprised of T2 weighted, diffussion weighted and dynamic contrast enhanced imaging with eithr 1.5T and 3.0T . difussion b values - 0,150,500 and 1000. Positive MRI - PIRADS Score 3 and above Positive MRI - PIRADS score 4 and above For clinically significant disease Reference standard(s) Transperineal Template Mapping Biopsy minimum number of samples was 20 Definition for clinically significant cancer Several definitions were used for multiple analyses UCL definition 1 UCL definition 2 Primary definition used by the study Gleason score 4+3 Gleason score 3+4	patients selection and flow and timing Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
Aubin (2010)	PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial	Study type Cross-sectional study Study details Study location USA Study setting Study dates No details provided Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy Within 6 months of enrollment tPSA between 2.5ng/ml and 10.0ng/ml Exclusion criteria None reported Sample characteristics Sample size 1,072 participants Mean age (SD) not provided - ranged 50-70years Index test(s) Prostate Cancer Gene 3	Patient selection Unclear risk of bias No details provided on patient selection strategy - only they were the control arm of another study Index test Unclear risk of bias Thresholds similar to that from other published studies Reference standard Low risk of bias Matched the protocol and deemed to be best at classifying prostate cancer Flow and timing Unclear risk of bias All paricipants received the both tests Overall risk of bias Moderate Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Reference standard(s) Prostate biopsy - not specified Definition for clinically significant cancer Any cancer	
Auprich (2012)	A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy	Study type Associated Study 2x2 tables obtained from this systematic review - Cross-sectional study Study details Study location USA Study setting hospital Study dates Between July 2008 and July 2009 Sources of funding None declared Inclusion criteria presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE Patient aged 70 years or below	Patient selection Unclear risk of bias No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria Index test Unclear risk of bias it is not clear whether the index test were interpreted without the knowledge of the reference standard results. The thresholds were defined by the predefined sensitivity levels. Reference standard Unclear risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria

Short Title	Title	Study Characteristics	Quality Assurance
		Exclusion criteria tPSA >50ng/ml Sample characteristics Sample size 127 participants Mean age (SD) reported as median range 63 (50-70) years PSA ng/ml median (range) 5.3 (3.2-45.5) Index test(s) Total PSA %fPSA Reference standard(s) Systematic TRUS biopsy included both 12/14 cores	Overall risk of bias Moderate Due to uncertainities surrounding patient section and time lapse between the index test and reference standard Directness Directly applicable
Barbera (2012)	PCA3 score accuracy in diagnosing prostate cancer at repeat biopsy: our experience in 177 patients	Study type Prospective cohort study Study details Study location Italy Study setting Not reported Study dates January 2010 and March 2012 Sources of funding	Patient selection Unclear risk of bias No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria Index test Unclear risk of bias It is unclear if the index test was intepreted without the knowledge of the reference standard It is unclear how the thresholds were determined, however the cutoffs are similar

Short Title	Title	Study Characteristics	Quality Assurance
		None declared Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination An elevated PSA >10ng/ml Sample characteristics Sample size 177 participants Mean age (SD) Median (range) 64 (48-74) years PSA ng/ml 74 participants had serum PSA >10ng/ml 99 between 4-10ng/ml 4 between 2.6-4ng/ml Number of previous biopsies at least one prior biopsy Time since last biopsy Not reported Index test(s) Prostate Cancer Gene 3 Cut off of 20 and 35 Reference standard(s) Systematic prostate biopsy Performed transperineally	to other papers in the review Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The index test was carried out before the reference standard, however the authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Due to uncertainities surrounding patient section and time lapse between the index test and reference standard Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
Boesen (2018)	Multiparametric MRI in men with clinical suspicion of prostate cancer undergoing repeat biopsy: a prospective comparison with clinical findings and histopathology	Study type Cross-sectional study Study details Study location Denmark Study setting No details provided Study dates Betweeb September 2011 to September 2013 Sources of funding No financial support Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination A previous abnormal TRUS image No patients had previously undergone MPMRI Exclusion criteria Prostate cancer diagnosis contraindications for undergoing prostate biopsy or mpMRI Sample characteristics Sample size 289 participants %female n/a Median age (Range) 64 years (59-67)	Patient selection Unclear risk of bias A database was used to enrol participants, however the selection strategy was not detailed Index test Low risk of bias ".. All mpMRI underwent blinded evaluation by the same physicia who registered and scored all suspicious lesions..." using PIRADS V1 Reference standard Low risk of bias The reference standard matches protocol and is regarded as the "gold standard" "... cores were obtained systematically blinded to mpMRI findings.." Flow and timing Low risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		PSA ng/ml Median Range - 12.0 (8.3 - 19)ng/ml PSA density, ng/ml/ml Median (range) - 0.19 (0.13-0.29) Number of previous biopsies median range - 2 (1-6) (unclear if this is months or years) Index test(s) mp-MRI PSA density Threshold - >0.15ng/ml/ml MRI guided/influenced bioPSY T2 weighted, diffusion weighted image ad dynamic contrast enhanced was performed prior to rebiopsy. DWI b values - 0, 100,800,1400s/mm2 Reference standard(s) TRUS guided biopsy Definition for clinically significant cancer Any biopsy core with Gleason score >6 Maximum cancer core length of at least 50% For Trus biopsy only - presence of at least 3 prostate cancer positive cores	
Busetto (2013)	Prostate cancer gene 3 and multiparametric magnetic resonance can reduce unnecessary biopsies:	Study type Prospective cohort study	Patient selection Low risk of bias The study particiants were consecutively enrolled to the study. he study was not of a case control design, all patients had both tests done. The authors did not state any

Short Title	Title	Study Characteristics	Quality Assurance
	decision curve analysis to evaluate predictive models	Study details Study location Italy Study setting Not reported Study dates March 2010 and July 2012 Sources of funding None disclosed Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer A persistently elevated or rising serum total PSA level Between 4-10ng/ml Exclusion criteria Prostate cancer diagnosis patients with missing data patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment An inadequalte proste biopsy with <10 cores Sample characteristics Sample size 171 participants Mean age (SD) 66.4 (5.3) years PSA ng/ml	inappropriate exclusion criteria Index test Low risk of bias It is unclear if the index test was intepreted without the knowledge of the reference standard It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		6.8 (1.6)ng/ml Index test(s) Prostate Cancer Gene 3 3 cut off - 27,35 and 50 mp-MRI Digital rectal examinatio (DRE) Reference standard(s) Systematic TRUS biopsy	
Chen (2011)	PSA density as a better predictor of prostate cancer than percent-free PSA in a repeat biopsy	Study type Cross-sectional study Study details Study location China Study setting Hospital Study dates From April 1999 to February 2008 Inclusion criteria At least one negative TRUS biopsy Abnormal digital rectal examination An elevated PSA PSA between 4 and 10.0 ng/ml Exclusion criteria Abnormal DRE	Patient selection Unclear risk of bias Patient selection stratedy was not detailed Index test Unclear risk of bias All patients had their index tests taken and calculated in the same way. The thresholds were not predetermined and the AUC was used to determine the optimum cut off Reference standard Low risk of bias The reference standard matched the protocol. All the participants had the same reference standard. It is unclear if the results were interpreted without the knowledge of index test results Flow and timing Unclear risk of bias The authors did not provide the time lapse between the

Short Title	Title	Study Characteristics	Quality Assurance
		And PSA levels >10ng/ml Sample characteristics Sample size 212 men Mean age (SD) 66.59 (9.92) years PSA ng/ml 6.34 (1.66) ng/ml PSA density, ng/ml/ml 0.182 (0.203) ng/ml/ml Index test(s) Total PSA Serum tPSA and free PSA (fPSA) were measured using TPSA-RIACT and FPSA-RIACT kits (CIS-Bio International, France), respectively %fPSA PSAV For the determination of PSAV, the latest three values of tPSA were obtained, and PSAV was calculated using linear regression PSA density Reference standard(s) TRUS biopsy TRUS-guided prostate biopsy was performed using an 18-G needle. The number of core biopsy specimens in the first and second TRUS-guided prostate biopsy was the same.	reference standard and index tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Moderate Due to uncertainities surrounding threshold setting, patient selection and blinding Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		The number was between 8 and 14. Definition for clinically significant cancer Definition was not provided	
Ciatto (2008)	PSA doubling time as a predictor of the outcome of random prostate biopsies prompted by isolated PSA elevation in subjects referred to an outpatient biopsy facility in a routine clinical scenario	Study type Cross-sectional study Study details Study location Italy Study setting Hospital Study dates January 2001 to August 2007 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy Negative digital rectal examination (defined as benign) PSA between 4 and 10.0 ng/ml Exclusion criteria None reported Sample characteristics Sample size 355 participants Median age (Range)	Patient selection Low risk of bias Consecutive patients were selected .. Index test Unclear risk of bias it is unclear how thresholds were determined but these were adopted apriori Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Low risk of bias total and f/t psa were tested immediately prior to biopsy using the Hybritech Tandem MP PSA Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		68 years (49-85years) Index test(s) Total PSA PSAV PSA density Free/Total PSA ratio Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	
Gittelman (2013)	PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study	Study type Prospective cohort study Study details Study location USA Study setting Community clinic Study dates Not reported Sources of funding Genprobe Inclusion criteria At least one negative TRUS biopsy 50 years and older	Patient selection Unclear risk of bias patient selection strategy not reported Index test Low risk of bias No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The thresholds were predetemined based on previously published studies Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard

Short Title	Title	Study Characteristics	Quality Assurance
		Exclusion criteria Prostate cancer diagnosis Any medication which can lower PSA levels Clinical symptoms of urinary tract infection History of invasive therapy for benign prostatic hyperplasia Participation in treatment studies within 6 months Sample characteristics Sample size 466 participants Mean age (SD) to add from supplement PSA ng/ml to add from supplement PSA density, ng/ml/ml to add from supplement Mean prostate volume to add from supplement Index test(s) Prostate Cancer Gene 3 Reference standard(s) TRUS biopsy and MP-MRI biopsy	Flow and timing Low risk of bias samples were collected 24 hrs of each other, if not possible within 7 days. The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Due to uncertainities surrounding patient section and time lapse between the index test and reference standard Directness Directly applicable
Gnanapragasam (2016)	The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant	Study type Retrospective cohort study	Patient selection Unclear risk of bias Patient selection strategy was not detailed

Short Title	Title	Study Characteristics	Quality Assurance
	prostate cancers in a repeat biopsy population	Study details Study location United Kingdom Study dates Between 2013 and 2015 Inclusion criteria At least one negative TRUS biopsy Exclusion criteria Presence of general contraindications for MRI patients with any suspicion of extracapsular extension any infection, prostatitis or previous prostate surgery Sample characteristics Sample size 279 people Mean age (SD) 66 years (range 45-80) Index test(s) Prostate health index Reference standard(s) Transperineal Template Mapping Biopsy Definition for clinically significant cancer Any cancer	Index test High risk of bias No PHI threshold was predetermined, the AUC curve was used to determine optimum threshold Reference standard Low risk of bias the reference standard was the one chosen by the committee as gold standard Flow and timing Low risk of bias The blood to asses the PHI was taken prior to any biopsies and at least 4 weeks prior to any prostate manipulation Overall risk of bias Moderate due to unclear patient selection strategy and the authors did not set any thresholds prior to the study Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
Goode (2013)	Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients	Study type Associated Study Obtained the 2x2 tables from this paper -: Retrospective cohort study Study details Study location USA Study setting Not reported Study dates Not reported Sources of funding None disclosed Inclusion criteria At least one negative TRUS biopsy Abnormal digital rectal examination An elevated PSA presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation Exclusion criteria Prostate cancer diagnosis Sample characteristics Sample size 456 participants Mean age (SD) reported as median (range) 66(41-90) years PSA ng/ml	Patient selection Unclear risk of bias No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria Index test Unclear risk of bias It is unclear if the index test was intepreted without the knowledge of the reference standard It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The index test was collected prior to the reference standard, however it is unclear what the time lapse was between the two tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Due to uncertainities surrounding patient section and time lapse between the index test and reference standard

Short Title	Title	Study Characteristics	Quality Assurance
		reported as median (range) 4.80 (0.1 - 54.2) ng/ml Number of previous biopsies up tp 5 biopsies, however majority of participants had 1 biopsy Index test(s) Prostate Cancer Gene 3 Reference standard(s) Systematic TRUS biopsy	Directness Directly applicable
Haese (2008)	Clinical Utility of the PCA3 Urine Assay in European Men Scheduled for Repeat Biopsy	Study type Prospective cohort study Study details Study location Six European centres -Germany, France, The Netherlands, Belgium and Austria Study setting Hospitals Study dates Between August and July 2007 Sources of funding Gen Probe Inc. Inclusion criteria At least one negative TRUS biopsy Exclusion criteria Any medication which can lower PSA levels	Patient selection Unclear risk of bias Patient selection was not detailed in termas of sampling strategy Index test Low risk of bias Specimens for the index tests were collected before the biopsies, The authors used three different thresholds for PCA3 and one for %fPSA. The thresholds were predetermined and in line with those from similar studies Reference standard Low risk of bias The reference standard matched the protocol and regarded as the gold standard. It is not clear if the results were intepreted in a blinded fashion

Short Title	Title	Study Characteristics	Quality Assurance
		Clinical symptoms of urinary tract infection Patients with atypia or prostatic intraepithelia neoplasia at any biopsy were excluded Men with more than 2 previous negative biopsies Sample characteristics Sample size 463 participants Mean age (SD) 64.4 (6.6) years PSA ng/ml Mean 8.9 (7.5)ng/ml Number of previous biopsies 331 participants had 1 biopsy 126 participants had 2 biopsies Index test(s) Prostate Cancer Gene 3 The PCA3 was calculated as [PCA3 mRNA]/[PSA mRNA]x1000 Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	Flow and timing Unclear risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Moderate Moderate – as a result of the uncertainties surrounding patients selection and index test results interpretation Directness Directly applicable
Kaufmann (2016)	Prostate cancer gene 3 (PCA3) is of additional predictive	Study type Retrospective cohort study	Patient selection Unclear risk of bias

Short Title	Title	Study Characteristics	Quality Assurance
	value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer.	Study details Study location Germany Study dates Between 2008-2014 Sample characteristics Sample size 49 patients Mean age (SD) 65 (5.6) years PSA ng/ml 10 (4.4) ng/ml PSA density, ng/ml/ml 0.22 (0.12) ng/ml/g Number of previous biopsies 1.7 (0.9) biopsies median interval of time between the first and last PSA assay 6 (3) months Index test(s) Prostate Cancer Gene 3 cut off of 25 and 35 Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided Any cancer	the patient selection strategy was not detailed Index test Low risk of bias the threshold was chosen based on evidence from similar studies. operators perfoming the PCA3 assay assessment were blinded to the patient's status Reference standard Low risk of bias the referene standard was the one chosen by the committee as a gold standard Flow and timing Unclear risk of bias the time between treatments was not detailed. Overall risk of bias Moderate as result of the lack of detail regarding patient selection Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
Keetch (1996)	Prostate specific antigen density versus prostate specific antigen slope as predictors of prostate cancer in men with initially negative prostatic biopsies	Study type Cross-sectional study Study details Study location USA Study setting No details provided Study dates Beginning July 1989 Sources of funding None declared Inclusion criteria Abnormal digital rectal examination An elevated PSA A previous abnormal TRUS image At least 2 prostate biopsies Exclusion criteria Patients with atypia or prostatic intraepithelia neoplasia at any biopsy were excluded Sample characteristics Sample size 327 participants Mean age (SD) 68 (6) years PSA ng/ml Median 6.8 ng/ml (SIR 1.9)	Patient selection Unclear risk of bias The study population was via a newspaperr article and only men who responded were included in the study. Index test Low risk of bias The index test were obtained prior to the reference standard. The thresholds were predetermined and were simialr to those from similar studies Reference standard Low risk of bias The reference standard matched the protocol, it was carried out after the index tests, it is not clear is the results from the index tests were blinded when interpreting reference standard results. Flow and timing Unclear risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Index test(s) PSA density was calculated by dividing the serum PSA at initial biopsy by the TRUS determined prostate volume at initial biopsy PSA slope PSA slope was determined by subtracting the PSA valueat the inintial screening visit from that at the most recent biopsy divided by the years between these 2 values Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	
Lazzeri (2012)	Serum index test %[-2]proPSA and Prostate Health Index are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy	Study type Cross-sectional study Study details Study location Italy Study setting Not declared Study dates June 2010 and June 2011 Sources of funding No financial support declared, however Unicel Dxl 800 Immuniassay Aystem analyzer p2PSA ([-2]proPSA) reagents were provided by Beckman Coulter Inc and Beckman Coulter	Patient selection Unclear risk of bias Men who were scheduled for repeat biopsy, no specific patient selection was detailed Index test Unclear risk of bias The thresholds were not chosen apriori. Reference standard Low risk of bias the reference standard was similar to the one identified in the protocol as the gold standard

Short Title	Title	Study Characteristics	Quality Assurance
		Italy Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation Exclusion criteria patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment Previous prostate treatment (i.e. transurethral prostate resection) Prostatits and underwent urethral catheterisation Sample characteristics Sample size 222 participants Mean age (SD) 63.9 years (7.1) PSA ng/ml Median (range) 7.6ng/ml, (0.3-46.4) PSA density, ng/ml/ml Median (range) 0.11 (0.02-0.91) ng/ml/ml Index test(s) Total PSA %fPSA	Flow and timing Low risk of bias Index test measurements were taken at the same time as the prepeat biopsy Overall risk of bias Moderate due to unclear patient selection and no apriori determination of index test thresholds Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Prostate health index Beckman-Coulter phi using the formula p2PSA/fPSA x square root of tPSA p2PSA,%p2PSA derived using the formula (p2PSA pg/ml/fPSA ng/ml x 1,000)x100 Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	
Lista (2015)	Multiparametric magnetic resonance imaging predicts the presence of prostate cancer in patients with negative prostate biopsy	Study type Prospective cohort study Study details Study location Spain Sources of funding FIS grant Inclusion criteria At least one negative TRUS biopsy An elevated PSA >4 ng/ml Sample characteristics Sample size 150 Mean age (SD)	Patient selection Unclear risk of bias Unclear how the patients were selected. All patients underwent both trials to avoid a case-control design. The authors did not state any inappropriate exclusion criteria. Index test Unclear risk of bias It is unclear if the index test was intepreted without the knowledge of the reference standard. The thresholds were pre-specified. Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard

Short Title	Title	Study Characteristics	Quality Assurance
		66.2 (5) PSA ng/ml 11.3 (9.6) Time since last biopsy 3 - 6 months Index test(s) mp-MRI Reference standard(s) TRUS biopsy	Flow and timing Unclear risk of bias The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Directness Directly applicable
Marks (2007)	PCA3 Molecular Urine Assay for Prostate Cancer in Men Undergoing Repeat Biopsy	Study type Cross-sectional study Study details Study location Nothern American Sites Study setting Not reported Study dates between April 2004 and January 2006 Sources of funding None disclosed Inclusion criteria At least one negative TRUS biopsy An elevated PSA 2.5ng/ml or greater	Patient selection Low risk of bias Consecutive men, Index test Unclear risk of bias It is unclear if the index test was intepreted without the knowledge of the reference standard It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The authors did not state the time lapse between the 2 tests.

Short Title	Title	Study Characteristics	Quality Assurance
		Exclusion criteria None reported Sample characteristics Sample size 233 participants Mean age (SD) 64 years (7) PSA ng/ml 7.4 (4.3)ng/ml Mean prostate volume 49 (29)ml Index test(s) Prostate Cancer Gene 3 Reference standard(s) Systematic TRUS biopsy	All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Due to uncertainities surrounding patient section and time lapse between the index test and reference standard Directness Directly applicable
Merola (2015)	PCA3 in prostate cancer and tumor aggressiveness detection on 407 high-risk patients: a National Cancer Institute experience	Study details Study location Italy Study dates Between November 2009 and May 2011 Inclusion criteria At least one negative TRUS biopsy An elevated PSA Suspicious DRE	Patient selection Low risk of bias 407 consecutive men with 2 or more risk factors for prostate cancer and at least one negative biopsy were included in the study. The study was not of a case control design and no inappropriate exclusions were identified Index test Unclear risk of bias The sample tests were carried prior to biopsies however, it is not clear whether the interpretations were carried out prior to reference standard test. is is unclear if the thresholds were

Short Title	Title	Study Characteristics	Quality Assurance
		Exclusion criteria Prostate cancer diagnosis Any medication which can lower PSA levels Sample characteristics Sample size 407 participants Mean age (SD) reported separately for cancer/non cancer groups cancer median 71 years (sd27) non cancer median 69 years (sd31) PSA ng/ml reported separately for cancer/non cancer groups cancer median 7.53ng/ml (sd4.88) non cancer median 7.34 ng/ml(sd5.87) Index test(s) Prostate Cancer Gene 3 Total PSA unable to calculate 2x2 for this test %fPSA unable to calculate 2x2 for this test Reference standard(s) Saturation prostatic biopsy	prespecified, however the thresholds are similar to other studies appart from threshold 5 for PCA3 Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Due to uncertainities surrounding index tests thresholds and time lapse between the index test and reference standard Directness Directly applicable
Michielsen (1998)	Specificity and accuracy of TRUS-measured PSA-density and transition zone-	Study details Study location Belgium Study dates between October 1996 and September 1997 Sources of funding	Patient selection Unclear risk of bias no details provided - however these were individuals refereed to the department for eurological evaluation

Short Title	Title	Study Characteristics	Quality Assurance
	PSA in the diagnosis of prostate cancer	None declared Inclusion criteria Serum PSA below 15ng/ml Aged 57-83 years Exclusion criteria None reported Sample characteristics Sample size 59 people Mean age (SD) 67 years (no SD) PSA ng/ml 8.8 ng/ml (no SD) Mean prostate volume 44 ml (no SD) Index test(s) PSA density PSA transition zone Reference standard(s) Systematic TRUS biopsy	Index test Unclear risk of bias it is unclear if the index test were interpreted prior to the reference standard The threshold were based on evidence from previous studies Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias Uncler no details provided Overall risk of bias Moderate Due to the uncertainities surrounding patient selection, index test and flow and timing Directness Directly applicable
Murray (2016)	Head to Head Comparison of the Chun Nomogram, Percentage Free PSA and Primary	Study type Retrospective cohort study Study details Study location	Patient selection Unclear risk of bias Patient selection strategy was not detailed. The particicipants were folloed up following initial nesgative biopsies. the exclusion criteria was appropriate and we could

Short Title	Title	Study Characteristics	Quality Assurance
	Circulating Prostate Cells to Predict the Presence of Prostate Cancer at Repeat Biopsy	Chile Study setting Hospital Study dates January 2006 to December 2014 Sources of funding No funding details provided Inclusion criteria Abnormal digital rectal examination An elevated PSA PSA > 4ng/ml PSA velocity of >0.75ng/ml/year Index test(s) %fPSA Chun's Normogram Definition for clinically significant cancer Any cancer	not identify inappropriate exclusions Index test Low risk of bias Index tests were carried out soon after biopsy. The thresholds were predetermined and were simialr to those from previous studies Reference standard Low risk of bias All participants had the same reference standard. The reference standard matches protocol and is regarded as the "gold standard" Flow and timing Low risk of bias .."Repeat blood samples were taken immediately prior to the second prostate biopsy for the detection of circulating prostate cells..." Overall risk of bias Low Directness Directly applicable
Ohigashi (2005)	Prostate specific antigen adjusted for transition zone epithelial volume: the powerful predictor for	Study type Associated Study Horinaga Minoru, Nakashima Jun, Ishibashi Midori, Oya Mototsugu, Ohigashi Takashi, Marumo Ken, and Murai Masaru (2002)	Patient selection Low risk of bias "consecutive patients undergoing inititail biopsies were enrolled.."

Short Title	Title	Study Characteristics	Quality Assurance
	the detection of prostate cancer on repeat biopsy	Clinical value of prostate specific antigen based parameters for the detection of prostate cancer on repeat biopsy: the usefulness of complexed prostate specific antigen adjusted for transition zone volume. The Journal of urology 168(3), 986-90 Cross-sectional study Study details Study location Japan Study setting No details provided Study dates Between October 1997 and January 2000 Sources of funding No details provided Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination PSA > 4ng/ml PSA between 4 and 10.0 ng/ml Exclusion criteria Prostatits and underwent urethral catheterisation Sample characteristics Sample size 75 participants	Index test Low risk of bias "serum specimens for determining total PSA and free Psa were obtained prior to reference standards", thresholds were set using evidence from previous studies Reference standard Low risk of bias The reference standard matched the protocol, the reference standard ws carried out after the index test, however it is unclear if interpretation was blinded Flow and timing Unclear risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Mean age (SD) 67.6 years (6.7) PSA ng/ml Mean (sd) - 7.58(1.37) PSA density, ng/ml/ml 0.208 (0.076) ng/ml/cm3 Mean fPSA 0.189 (0.107) Index test(s) Total PSA PSA density Free/Total PSA ratio Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	
Okada (2010)	Community-based prostate cancer screening in Japan: Predicting factors for positive repeat biopsy	Study type Retrospective cohort study Study details Study location Japan Study setting Hospital Study dates 1995 and 2006 Sources of funding	Patient selection Unclear risk of bias Participants were selected from a screening program and had to meet specific inclusion criteria. The authours did not mention the exact patient selection strategy - i.e. whether or not random or consecutive patients were enrolled Index test Unclear risk of bias it is unclear if the index tests were intepreted without the knowledge of the reference standard. The thresholds were

Short Title	Title	Study Characteristics	Quality Assurance
		No funding details provided Inclusion criteria At least one negative TRUS biopsy An elevated PSA Exclusion criteria None reported Sample characteristics Sample size 140 participants Mean age (SD) 73.8 years (5.6) and 72.8 years (6.4) in the non cancer group PSA ng/ml Mean Initial PSA - 6.8 ng/ml (3.2) Mean Latest PSA - 15.1 ng/ml (19.5) and 10.2 (6.9) in the non cancer group PSA density, ng/ml/ml Mean initial PSAD - 0.30 ng/ml/ml (0.20) Mean latest PSAD - 0.55 ng/ml/ml (0.51) and 0.27ng/ml/ml (0.21) in the no cancer group	not prespecified. Reference standard Low risk of bias the reference standard was the one chosen by the committee as being able to correctly classify prostate cancer. Flow and timing Unclear risk of bias All participants included in the study received both tests. The index tests were done within the same time as the biopsy Overall risk of bias Moderate due to unclear patient selection strategy and the authors did not predetermine the index tests thresholds Directness Directly applicable
Okegawa (2003)	Predictors of prostate cancer on repeat prostatic biopsy in men with serum total prostate-specific antigen between 4.1 and 10 ng/mL	Study type Cross-sectional study Study details Study location Japan Study setting	Patient selection Unclear risk of bias The authors did not specify the patient selection strategy. The study was not of a case control design. Index test Unclear risk of bias

Short Title	Title	Study Characteristics	Quality Assurance
		Hospital Study dates Between 1997-2001 Loss to follow-up None mentioned Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy PSA > 4ng/ml Exclusion criteria None reported Sample characteristics Sample size 97 participants Mean age (SD) 64 (8.6) years PSA ng/ml 6.7 (2.0) ng/ml PSA density, ng/ml/ml 0.187 (0.102) ng/ml/ml Index test(s) Total PSA %fPSA PSAV PSA density	The index tests thresholds were not pre-specified. It is unclear if intepretations were carried without knowledge of the reference standard Reference standard Low risk of bias The reference matched the protocol and was thought to be able to slassify prostate cance as accurately as possible by the committee Flow and timing Unclear risk of bias All the participants received both the index tests and refernce standard. All the particiants were included in the analysis Overall risk of bias Moderate due to lacking details on patient selection strategy Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Reference standard(s) Prostate biopsy - not specified Definition for clinically significant cancer Any cancer	
Panebianco (2011)	PCA3 urinary test versus 1H-MRSI and DCEMR in the detection of prostate cancer foci in patients with biochemical alterations	Study type Prospective cohort study Study details Study location Italy Study setting Not disclosed Study dates September 2009 to February 2010 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Negative digital rectal examination (defined as benign) PSA between 4 and 10.0 ng/ml Exclusion criteria patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment	Patient selection Unclear risk of bias Patient selection details were not provided Index test Unclear risk of bias It is unclear if the index test was carried out bfore the biopsy. The threshold was predetermined and was similar to that from other papers investigating the same index test Reference standard Low risk of bias The reference standard matched that specified by the protocol. it is unclear if the resluts from the index tests were blinded before interpresting the reference standard Flow and timing Unclear risk of bias The authors did not provide the time lapse between the reference standard and index tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Moderate

Short Title	Title	Study Characteristics	Quality Assurance
		Sample characteristics Sample size 41 participants Mean age (SD) 60.3 years (48-69 years) PSA ng/ml Mean 6.37ng/ml Index test(s) Prostate Cancer Gene 3 Reference standard(s) TRUS biopsy	Due to uncertainities surrounding patient section, blinding of results and time lapse between the index test and reference standard Directness Directly applicable
Pepe (2011)	PCA3 score vs PSA free/total accuracy in prostate cancer diagnosis at repeat saturation biopsy	Study type Cross-sectional study Study details Study location Italy Study setting Hospital Study dates From October 2009 to September 2011 Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination	Patient selection Low risk of bias "...74 consecutive Caucasian men aged between 48 and 74 years.." Index test Low risk of bias The index test was taken before the biopsy, the study had two thresholds, both predetermined and simialr to studies of a similar nature Reference standard Unclear risk of bias The reference standard matched protocol and regarded as the gold standard.

Short Title	Title	Study Characteristics	Quality Assurance
		Sample characteristics Sample size 102 participants Mean age (SD) median age 64.5 yrs; range: 58-71 yrs) Index test(s) Prostate Cancer Gene 3 PSA ratio Reference standard(s) TRUS biopsy The prostate biopsy protocol included a median of 12 cores in the posterior zone of each lobe (apex, median zone and base of the gland) beginning parasagittally to reach the outer edges of the gland (lateral margins) and 2-3 cores in the transition zone	Flow and timing Low risk of bias Three-ten days before performing the SPBx, first-catch urine samples were collected following DRE (three strokes per lobe) and processed to quantify PCA3 and PSA mRNA concentrations using the Progensa PCA3 assay Overall risk of bias Moderate Directness Directly applicable
Pepe (2012)	PCA3 score and prostate cancer diagnosis at repeated saturation biopsy. Which cut-off: 20 or 35?	Study type Prospective cohort study Study details Study location Italy Study setting Hospital Study dates January 2010 to May 2011 Sources of funding	Patient selection Low risk of bias the patients were consecutve patients meeting the protocol.the study was not of a case-control design or patients had biomarkers taken and had biopsies Index test Unclear risk of bias First catch samples of urine were caught following digital rectal examination, 3-10 days prior to biopsy, it is unclear if the results were interpreted prior to biopsy

Short Title	Title	Study Characteristics	Quality Assurance
		None declared Inclusion criteria At least one negative TRUS biopsy Abnormal digital rectal examination All patients had a negative DRE An elevated PSA PSA> 10ng/ml, PSA values between 4.1 - 10 or 2.6-4ng/ml with free/total PSA </= 25% and </= 20% respectively. Exclusion criteria Prostate cancer diagnosis Sample characteristics Sample size 118 participants Mean age (SD) median 62.5 years (no range or sd) PSA ng/ml Median PSA 8.5 ng/ml (3.7-24ng/ml) Time since last biopsy 9 months Index test(s) Prostate Cancer Gene 3 From 3-10 days prior to performing SPBx, first catch urine samples were collected following DRE, and processed to quantify PCA3 and PSA mRNA concentrations using the PROGENSA PCA3 assay	Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Low risk of bias First catch samples of urine were caught following digital rectal examination, 3-10 days prior to biopsy All patients received the same reference standard All patients were included in the analysis Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Reference standard(s) Systematic prostate biopsy performed transperineally using a tru-cut 18 gauge needle supplied with a biplanar transrectal probe under sedation and antibiotic prophylaxis	
Pepe (2013)	Prostate cancer detection rate at repeat saturation biopsy: PCPT risk calculator versus PCA3 score versus case-finding protocol	Study type Associated Study Unable to source- data obtained from systematic review	
Porpiglia (2014)	The roles of multiparametric magnetic resonance imaging, PCA3 and prostate health index-which is the best predictor of prostate cancer after a negative biopsy?	Study type Prospective cohort study Study details Study location Italy Study setting Hospital Study dates Between March 2011 and April 2013 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy Positive Digital rectal examination	Patient selection Unclear risk of bias No details provided Index test Low risk of bias All patients underwent pca3 testing before random biopsy Single experienced radiologist analyzed the mp-MRI findings. The radiologist was blinded to the pathologist biopsy reports and to the biomarker results. The cutoffs for PCA3 and PHI in our cohort were obtained using ROC analysis - therefore not predetermined Reference standard Low risk of bias The reference standard was chosen by the committee and

Short Title	Title	Study Characteristics	Quality Assurance
		Exclusion criteria contraindications for undergoing prostate biopsy or mpMRI Previous prostate treatment (i.e. transurethral prostate resection) Patients suspected to have anterioly located PCA Sample characteristics Sample size 170 participants Mean age (SD) Median age (iqr) 65 years (60-70) Index test(s) mp-MRI All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil. Functional information was obtained by DWI and dynamic contrast enhanced MRI. Total PSA %fPSA All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California)16 after processing with a Unicel DxI 800 Immunoassay System analyzer (Beckman Coulter).	was regarded as gold standard Flow and timing Unclear risk of bias No details provided Overall risk of bias Moderate No details provided on patient selection and the thresholds dor biomarkers was determined by the ROC curve and not prior analysis Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Prostate health index Reference standard(s) Random Biopsy under TRUS	
Remzi (2003)	An artificial neural network to predict the outcome of repeat prostate biopsies	Study type Cross-sectional study Study details Study location Austria Study setting Not detailed Study dates January 1997 to January 2001 Sources of funding Not declared Inclusion criteria At least one negative TRUS biopsy PSA between 4 and 10.0 ng/ml Sample characteristics Sample size 820 patients Mean age (SD) 68years (8.5) PSA ng/ml Mean 6.4 ng/ml (1.8) PSA density, ng/ml/ml 0.156 ng/ml/ml (0.007)	Patient selection Low risk of bias The patients were enrolles as consecutive referrals for early prostate cancer detection Index test Unclear risk of bias thresholds were not prespecified, however were determined using the 95% sensitivity threshold Reference standard Low risk of bias the reference standard matched protocol and was deemed to be the optimal to correctly classify the target condition Flow and timing Low risk of bias All the included participants received both tests. The tests were taken within the same time scale Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Time since last biopsy 6 weeks Index test(s) Total PSA PSA density PSA transition zone Free/Total PSA ratio Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	
Remzi (2010)	Follow-up of men with an elevated PCA3 score and a negative biopsy: does an elevated PCA3 score indeed predict the presence of prostate cancer?	Study type Associated Study Haese A, de la Taille , A , van Poppel , H , Marberger M, Stenzl A, Mulders P F. A, Huland H, Abbou C C, Remzi M, Tinzl M, Feyerabend S, Stillebroer A B, van Gils , M P M. Q, and Schalken J A (2008) Clinical Utility of the PCA3 Urine Assay in European Men Scheduled for Repeat Biopsy. European Urology 54(5), 1081-1088 The 2x2 tables were extracted rom this systematic review - Cross-sectional study Study details Study location Austria	Patient selection Low risk of bias No details were provided for this study. it is linked to the Haese study. see QA for Haese Index test Unclear risk of bias It is unclear if the index test was intepreted without the knowledge of the reference standard It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review. Reference standard Low risk of bias The reference standard was chosen by the committee and

Short Title	Title	Study Characteristics	Quality Assurance
		Study setting Hospital Study dates Not reportee See Haese et al Sources of funding None disclosed Inclusion criteria presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE Suspicious imaging results low %free PSA Follow up biopsy Exclusion criteria None reported Sample characteristics Sample size 463 participants Index test(s) Prostate Cancer Gene 3 Reference standard(s) Prostate biopsy - not specified	was regarded as gold standard Flow and timing Low risk of bias The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Details of the study not fully explained, study linked to Haese 2008 Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
Scattoni (2013)	Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy	Study type Prospective cohort study Study details Study location Italy Study setting Not disclosed Study dates Decembr 2011 and May 2012 Sources of funding Beckman Coulter provided access Hybritech p2PSA reagents and the Access 2 immunoassay system. No financial support declared Inclusion criteria presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation PSA between 4 and 15 ng/ml Exclusion criteria None reported Sample characteristics Sample size 95 participants Mean age (SD) 67.7 years (7.3) PSA ng/ml	Patient selection Low risk of bias "Consecutive cohort of European men scheduled for repeat biopsy" Index test Unclear risk of bias it is not clear whether the index test were interpreted without the knowledge of the reference standard results. Reference standard Low risk of bias The reference standard was matched the one chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The blood sample was drown at biopdt just before prostatic manipulations Overall risk of bias Moderate Due to uncertainities surrounding patient section and time lapse between the index test and reference standard Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		9.8 ng/ml (3.9) Index test(s) Prostate Cancer Gene 3 %fPSA PSAV Prostate health index Reference standard(s) TRUS biopsy	
Shaida (2009)	The chances of subsequent cancer detection in patients with a PSA > 20 ng/ml and an initial negative biopsy	Study type Cross-sectional study Study details Study location UK Study setting Hospital Study dates between 1997 and 2002 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy An elevated PSA >20ng/ml Sample characteristics Sample size	Patient selection Unclear risk of bias No details were provided regarding patient selection strategy. Index test Unclear risk of bias The thresholds were not prespecified, these were determined using the ROC curve analysis Reference standard Low risk of bias The reference standard matched the protocol, and was deemed to be the best at identifying prostate cancer Flow and timing Low risk of bias All patients received both tests and the authors reported for all outcomes The tests were taken within the same time

Short Title	Title	Study Characteristics	Quality Assurance
		67 participants Index test(s) PSAV PSA density	frame Overall risk of bias Moderate Due to lack of patient strategy and index thresholds Directness Directly applicable
Shimbo (2009)	PSA doubling time as a predictive factor on repeat biopsy for detection of prostate cancer	Study type Cross-sectional study Study details Study location Japan Study setting Hospital Study dates From January 2004 to December 2005 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA in a range between 4 and 20 ng/ml Sample characteristics Sample size 77 cases	Patient selection Unclear risk of bias Sampling strategy was not detailed in terms of randomisation or consecitive participants Index test Unclear risk of bias It is unclear when and how the index test was carried out. Reference standard Low risk of bias The referebce standard was matched to the protocol and regarded as the gold standard. Flow and timing Unclear risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Moderate

Short Title	Title	Study Characteristics	Quality Assurance
		Mean age (SD) 72.4+6.6 years PSA ng/ml Initial tPSA (ng/ml) 7.2+2.7 tPSA (ng/ml) 10.2+3.8 PSA density, ng/ml/ml Mean 0.36+0.22ng/ml Index test(s) %fPSA %Free/tPSA was calculated from dividing free PSA by tPSA PSA doubling time Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided	as a result of the uncertainties surrounding patients selection and index test results interpretation Directness Directly applicable
Simmons (2017)	The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy	Study type Cross-sectional study Study details Study location UK Study dates 11 January 2012 to 29 January 2014 Sources of funding United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical	Patient selection Unclear risk of bias the patient selection strategy was not defined Index test Low risk of bias The radiologist was blinded to previous TRUS-biopsy results, but given the PSA level and any other risk factors The thresholds were predetermined, the authors used PIRADS scoring system and MPMRI greater than 3 were

Short Title	Title	Study Characteristics	Quality Assurance
		Research Centre. Inclusion criteria At least one negative TRUS biopsy Sample characteristics Sample size 249 completing both mpMRI and TTPM biopsies Mean age (SD) 62 (7) years PSA ng/ml 6.8 (4.8–9.8) ng/ml/ml Number of previous biopsies 1 (1–2) Median Prostate volume 37.0 (26.8–50.0) Index test(s) mp-MRI Using a 3 T magnetic field strength scanner with a pelvic-phased array coil. Magnetic resonance imaging sequences included T1-weighted, T2-weighted, diffusion weighting with high b-value (b¼2000) sequence and apparent diffusion coefficient map using multiple b-values (b¼0, 150, 500, 1000) and dynamic contrast enhancement with gadolinium Positive MRI - PIRADS Score 3 and above	deemed as positive of suspicious of cancer Reference standard Low risk of bias Patients were blinded to the mpMRI results tominimise non-compliance and selection bias All biopsies were reported by one of two expert uropathologists of 420 years of experience each who were blinded to the mpMRI reports Flow and timing Unclear risk of bias The authors did not mention any time lapses between the index test and the reference standard Overall risk of bias Low Directness Directly applicable

Short Title	Title	Study Characteristics	Quality Assurance
		Reference standard(s) Transperineal Template Mapping Biopsy Definition for clinically significant cancer Gleason pattern 4 or greater (i.e., Gleason X4þ3) or a CCL involvement of X6mm in any one location of any Gleason score	
Tsivian (2017)	Assessing clinically significant prostate cancer: Diagnostic properties of multiparametric magnetic resonance imaging compared to three-dimensional transperineal template mapping histopathology	Study type Retrospective cohort study Study details Study location USA Study setting No details provided Study dates 3 year period beginning in 2011 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA Exclusion criteria Prostate cancer diagnosis Sample characteristics Sample size	Patient selection Low risk of bias Authors state “...consecutive patients who underwent mpMRI followed by 3Dttmb” Index test Low risk of bias The index test was carried out before the reference standard. All image interpretation was carried out on a picture archiving and communication system by a single board -certified fellowship-trained radiologist with 5 years experience Authors state "Interpretation was carried out in a blinded fashion" mpMRI scores of 3-5 were considered positive - additional analysis of scores 3 and 4-5 were also included Reference standard Low risk of bias The reference standard matches protocol and is regarded as the "gold standard" Flow and timing Low risk of bias

Short Title	Title	Study Characteristics	Quality Assurance
		50 patients %female n/a Median age (Range) 65 (61-69) years PSA ng/ml Median (IQR) - 7.1 (5.1-13.6) Number of previous biopsies 1 - 23 participants 2/more - 27 participants Index test(s) mp-MRI Reference standard(s) Transperineal Template Mapping Biopsy Definition for clinically significant cancer Any biopsy core with Gleason score >6 Also UCL1 and UCl2 definition	The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Low Directness Directly applicable
Wu (2012)	Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer	Study type Retrospective cohort study Study details Study location USA Study setting hospital Study dates not declared Sources of funding	Patient selection Low risk of bias Consecutive patients were enrolled in the study. the study was not of a case-control design Index test Unclear risk of bias It is unclear if the biomaarker results were interpretted prior to the biopsy. the thresholds used were predetermined based on past litereature.

Short Title	Title	Study Characteristics	Quality Assurance
		None declared Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE Exclusion criteria None reported Sample characteristics Sample size 103 participants Mean age (SD) 63.5 years (7.4) PSA ng/ml 11.0 ng/ml (8.5) Index test(s) Prostate Cancer Gene 3 PSA density Reference standard(s) Systematic TRUS biopsy	Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Unclear risk of bias The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis Overall risk of bias Moderate Due to uncertainities surrounding time lapse between the index test and reference standard Directness Directly applicable

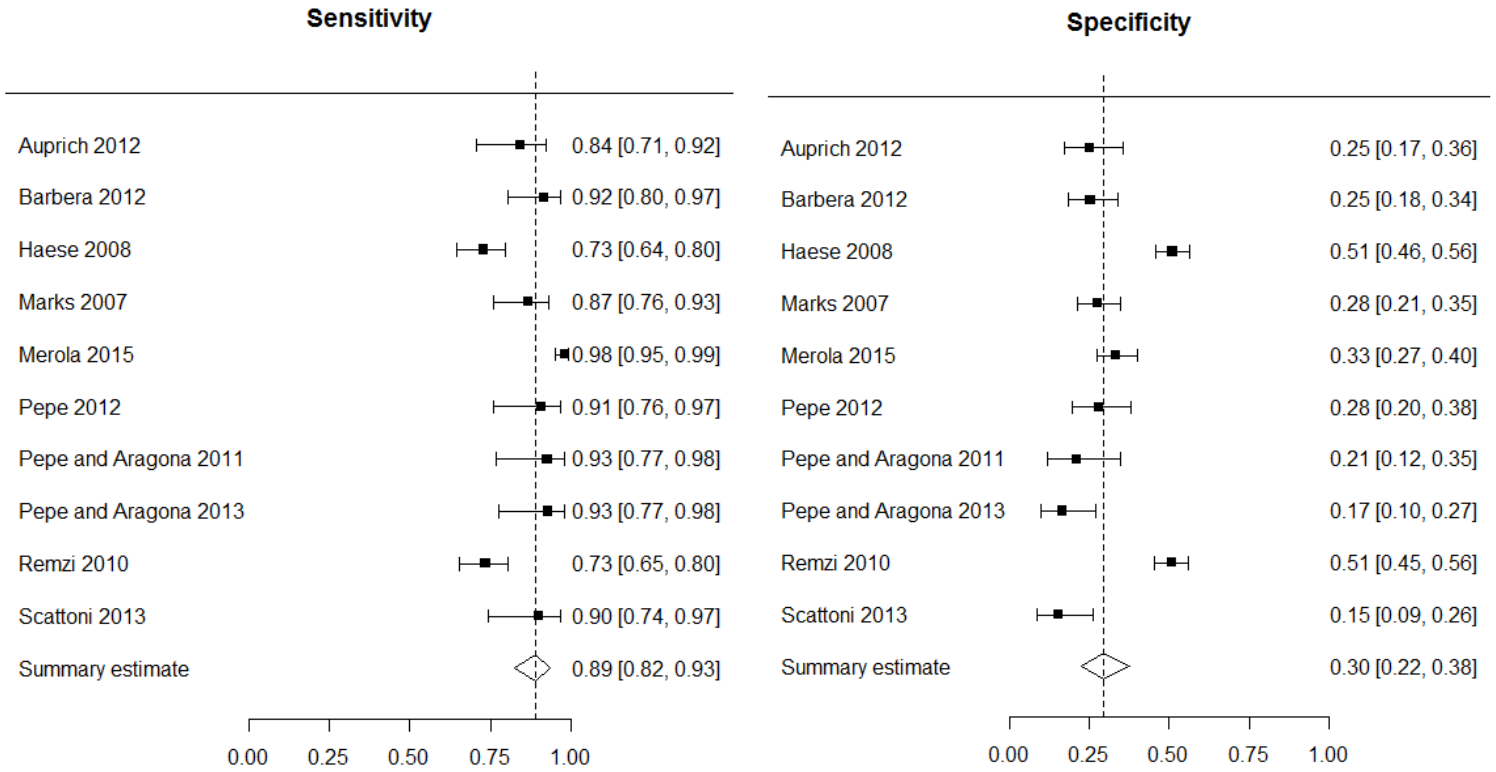
Short Title	Title	Study Characteristics	Quality Assurance
Yilmaz (2015)	Percentage of free prostate-specific antigen (PSA) is a useful method in deciding to perform prostate biopsy with higher core numbers in patients with low PSA cut-off values	Study type Retrospective cohort study Study details Study location Turkey Study setting Hospital Study dates between 2005 and 2011 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy tPSA between 2.5ng/ml and 10.0ng/ml Negative digital rectal examination (defined as benign) Exclusion criteria patients with missing data Prostatic radiation therapy A total number of biopsies less than or greater than 12 patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment Sample characteristics Sample size 605 participants Mean age (SD)	Patient selection Low risk of bias This was a retrospective study analysing participants from a data base, initially patients were consecutively selected fro their initial biopsy Index test Low risk of bias The index test thresholds were predetermined and the suthors used previously published figures to guide thire threshold selection. It is unclear if the index tests were done in a blinded manner Reference standard Low risk of bias The reference standard matched the protocol and was regarded as the gold standard by the committee. it is unclear if the reference standard was carried out in a blinded manner from the index test Flow and timing Unclear risk of bias The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis Overall risk of bias Low

Short Title	Title	Study Characteristics	Quality Assurance
		median age (IQR) - 65years (59-71) PSA ng/ml 6.3 (5.1-7.8)ng/ml Mean prostate volume 49.9cm3 (36.2-69.1) Mean fPSA 1.1 (IQR - 0.8-1.5)ng/ml Index test(s) %fPSA Different cut off points - 10%, 15%, 20%, 25% Reference standard(s) Systematic TRUS biopsy 12 core	Directness Directly applicable
Yuasa (2008)	Characterization of prostate cancer detected at repeat biopsy	Study type Cross-sectional study Study details Study location Japan Study dates Between 1998 and 2006 Sources of funding None declared Inclusion criteria At least one negative TRUS biopsy	Patient selection Unclear risk of bias No details provided on patient selection strategy Index test Unclear risk of bias Thresholds were detemined apriori, unclear if the interpretations were carried out without the knowledge of the reference standard results Reference standard Low risk of bias Reference matched protocol

Short Title	Title	Study Characteristics	Quality Assurance
		Exclusion criteria None reported Sample characteristics Sample size 127 patients Mean age (SD) (Only povided in those who had cancer) 72.0 (5.7) years PSA ng/ml Only reported in those with cancer 12.6 (8.6) ng/ml Index test(s) PSAV PSA density Reference standard(s) Prostate biopsy - not specified Definition for clinically significant cancer Any cancer	Flow and timing Low risk of bias All participants received both tests The measuremente were completed within the same time period Overall risk of bias Moderate Due to the uncertainities surrounding patient selection strategy Directness Directly applicable

Appendix F – Forest plots

Prostate cancer antigen 3 - Prostate cancer antigen 3 cut off 20 sensitivity and specificity



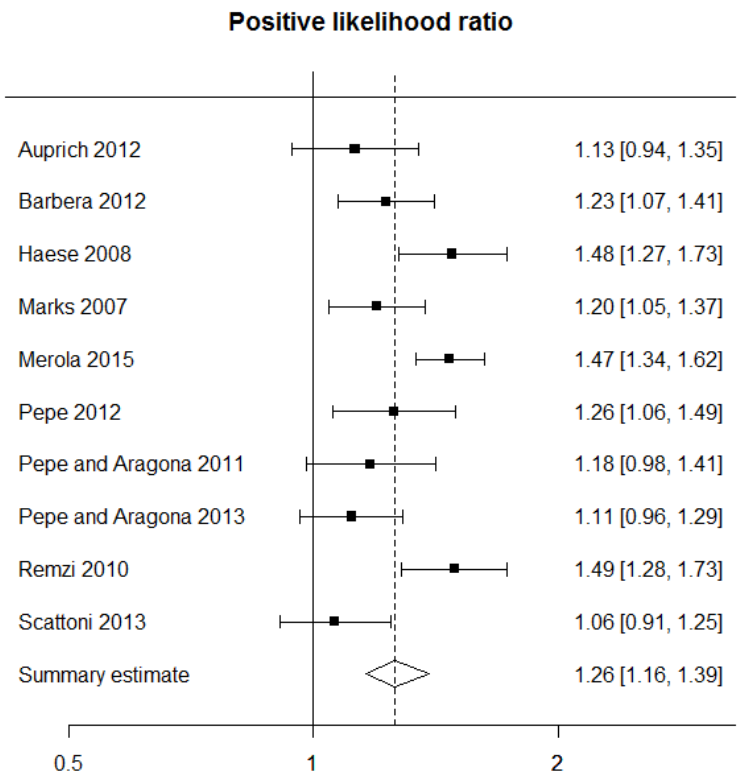
Heterogeneity, sensitivity:

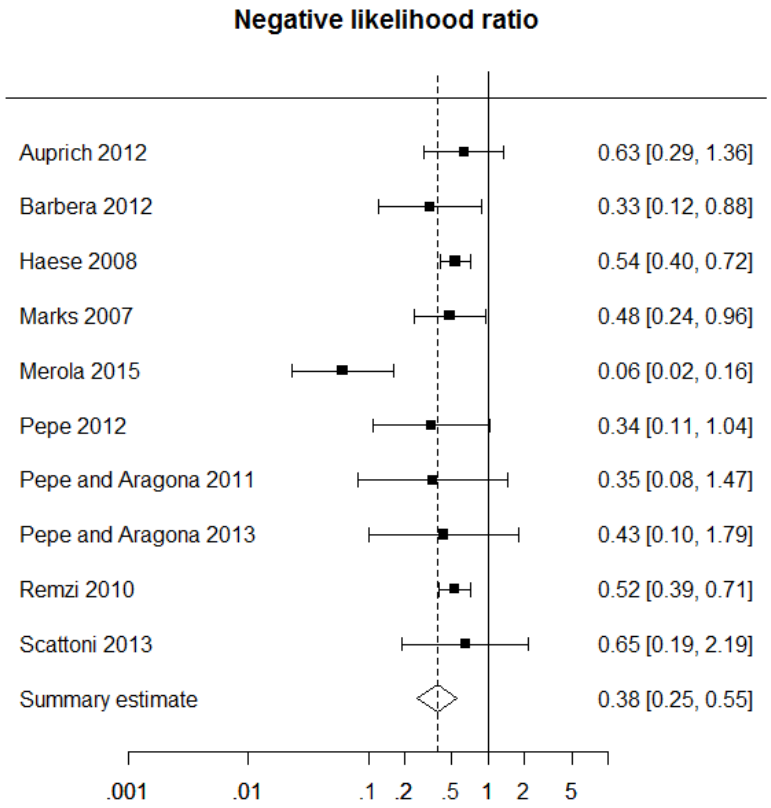
Tau^2 =0.59,Ch^2= 45.73, df=9 (p<0.001), I^2 = 80.3%

Heterogeneity, specificity

Tau^2 =0.33,Ch^2= 101.25, df=9 (p<0.001), I^2 = 91.1%

Prostate cancer antigen 3 cut off 20 (Reference standard Biopsy)





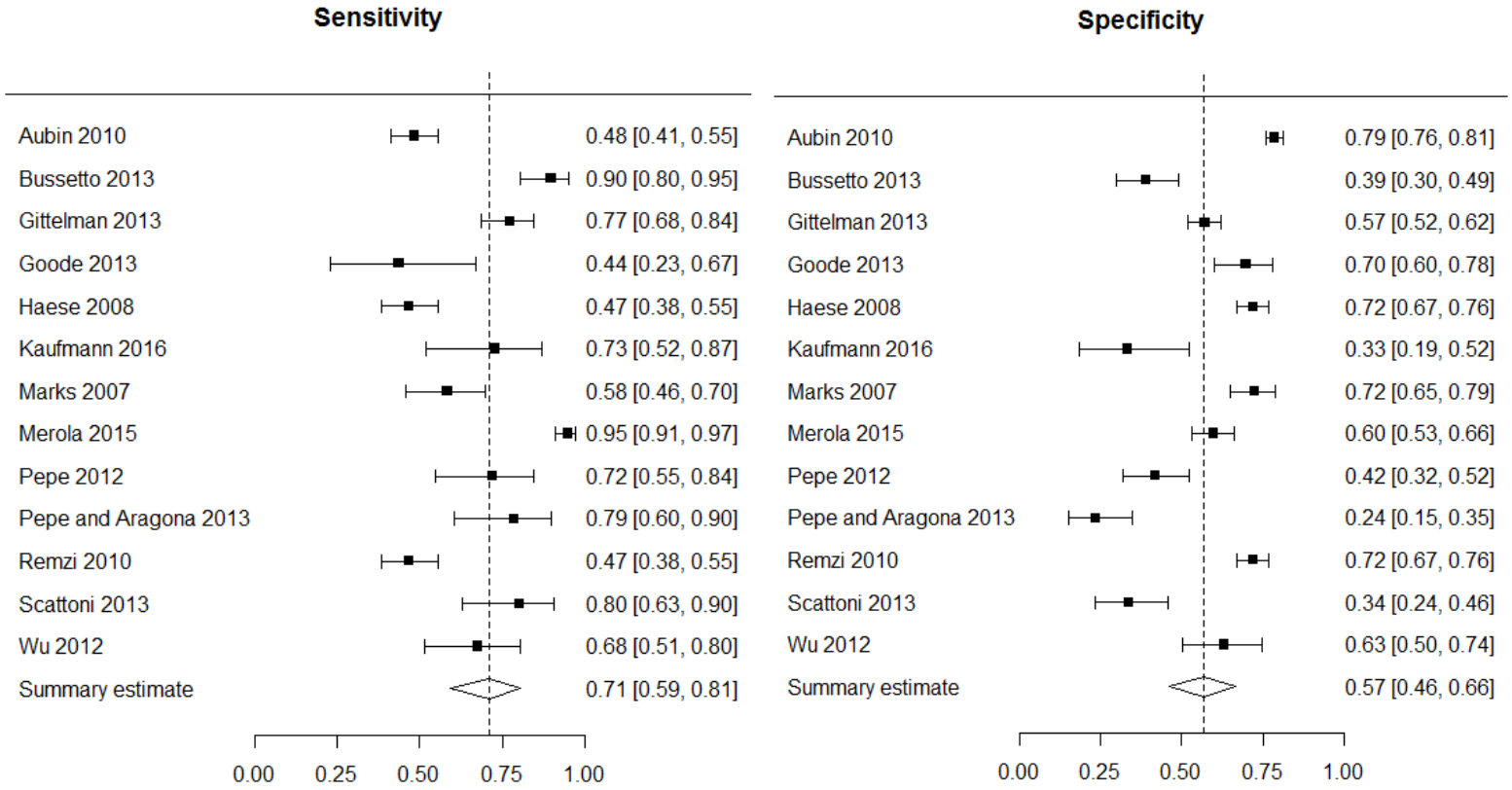
Heterogeneity, positive LR:

Tau^2 =0.13,Ch^2= 31.09, df=9 (p<0.001), I^2 = 71.1%

Heterogeneity, negative LR

Tau^2 =0.13, Ch^2= 20.12, df=9 (p<0.017), I^2 = 55.3%

Prostate cancer antigen 3 cut off 35 (Reference standard Biopsy) sensitity and specificity



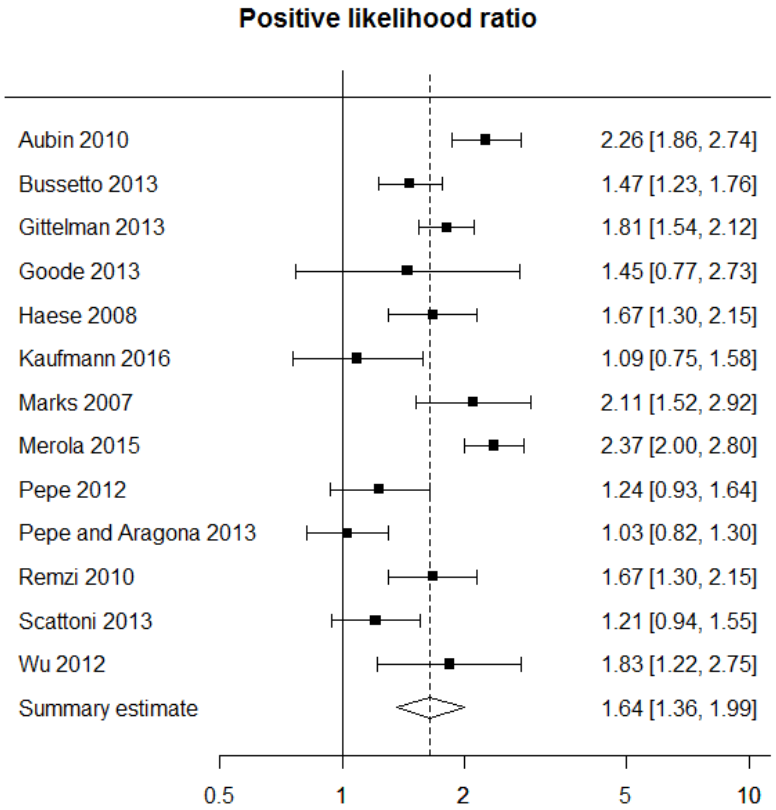
Heterogeneity, sensitivity:

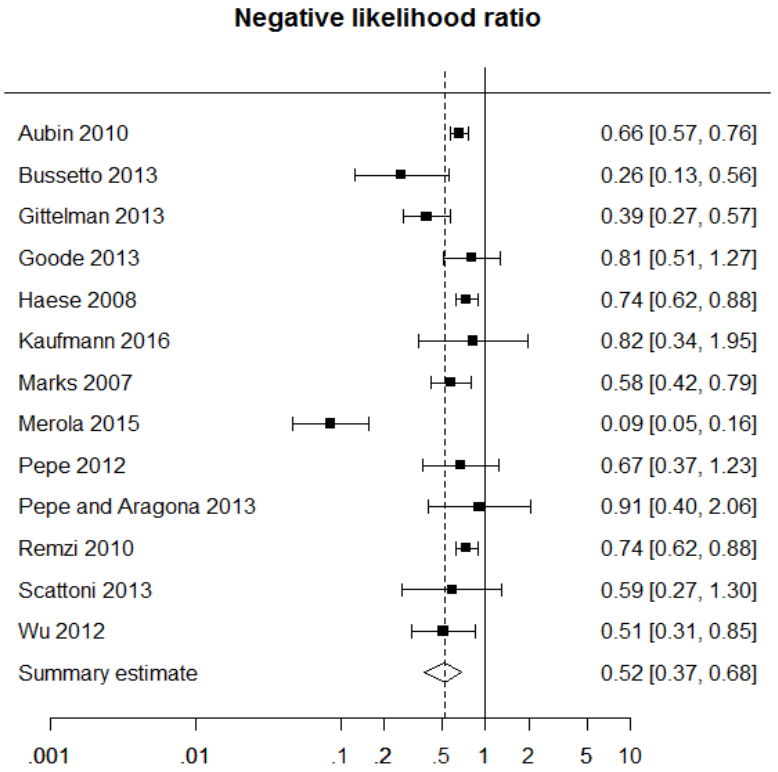
$Tau^2 = 0.74, Ch^2=133.93$, df=12 ($p<0.001$), $I^2 = 91.0\%$

Heterogeneity, specificity

$Tau^2 =0.42, Ch^2=219.64$, df=12 ($p<0.001$), $I^2 = 94.5\%$

Prostate cancer antigen 3 cut off 35 (Reference standard Biopsy) positive and negative likelihood ratio





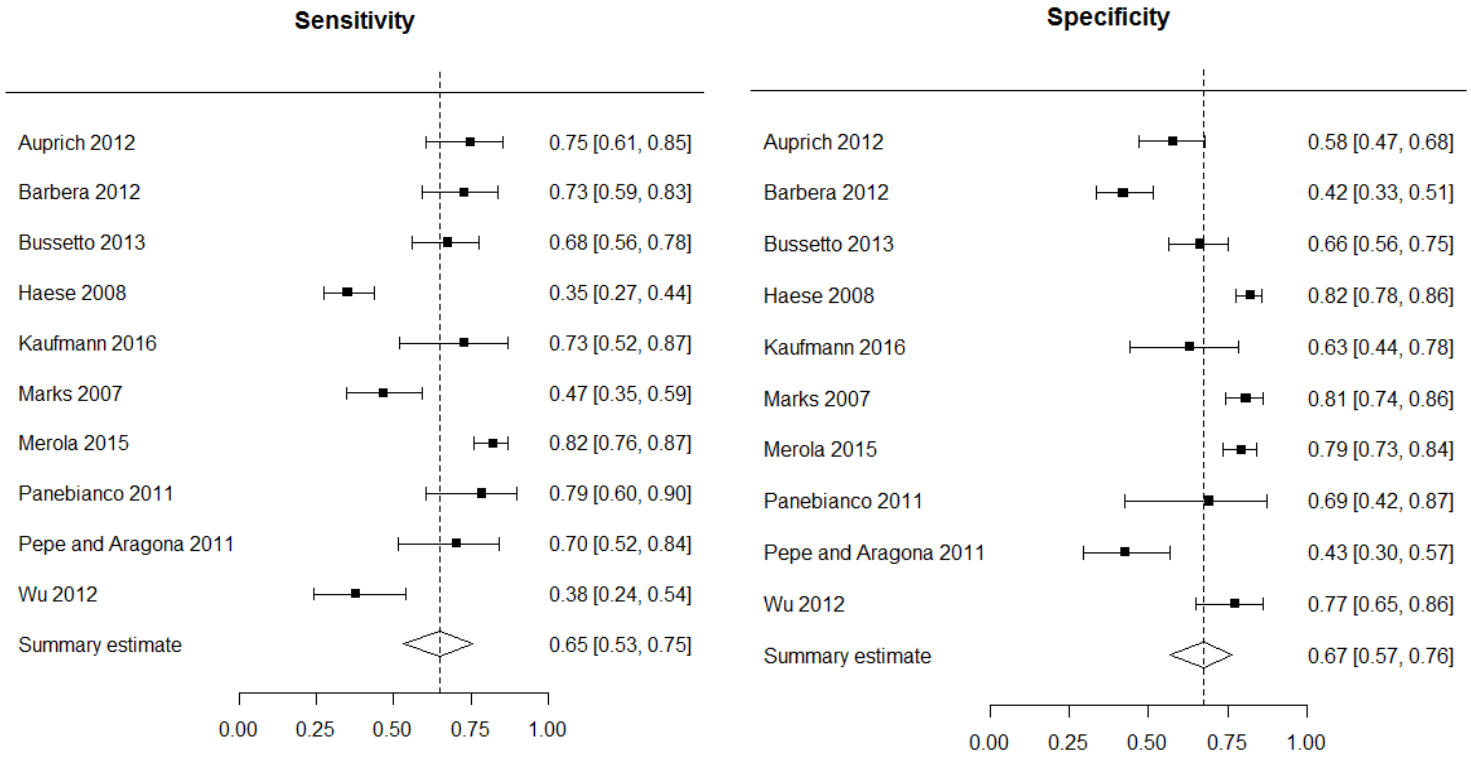
Heterogeneity, Positive LR:

Tau^2 = 0.06,Chi^2=, 63.83 df=12 (p<0.001), I^2 =81.2%

Heterogeneity, Negative LR

Tau^2 = 0.06,Chi^2=61.66 df=12 (p<0.001), I^2 =80.5%

Prostate cancer antigen 3 cut off 50 (Reference standard Biopsy) sensitivity and specificity



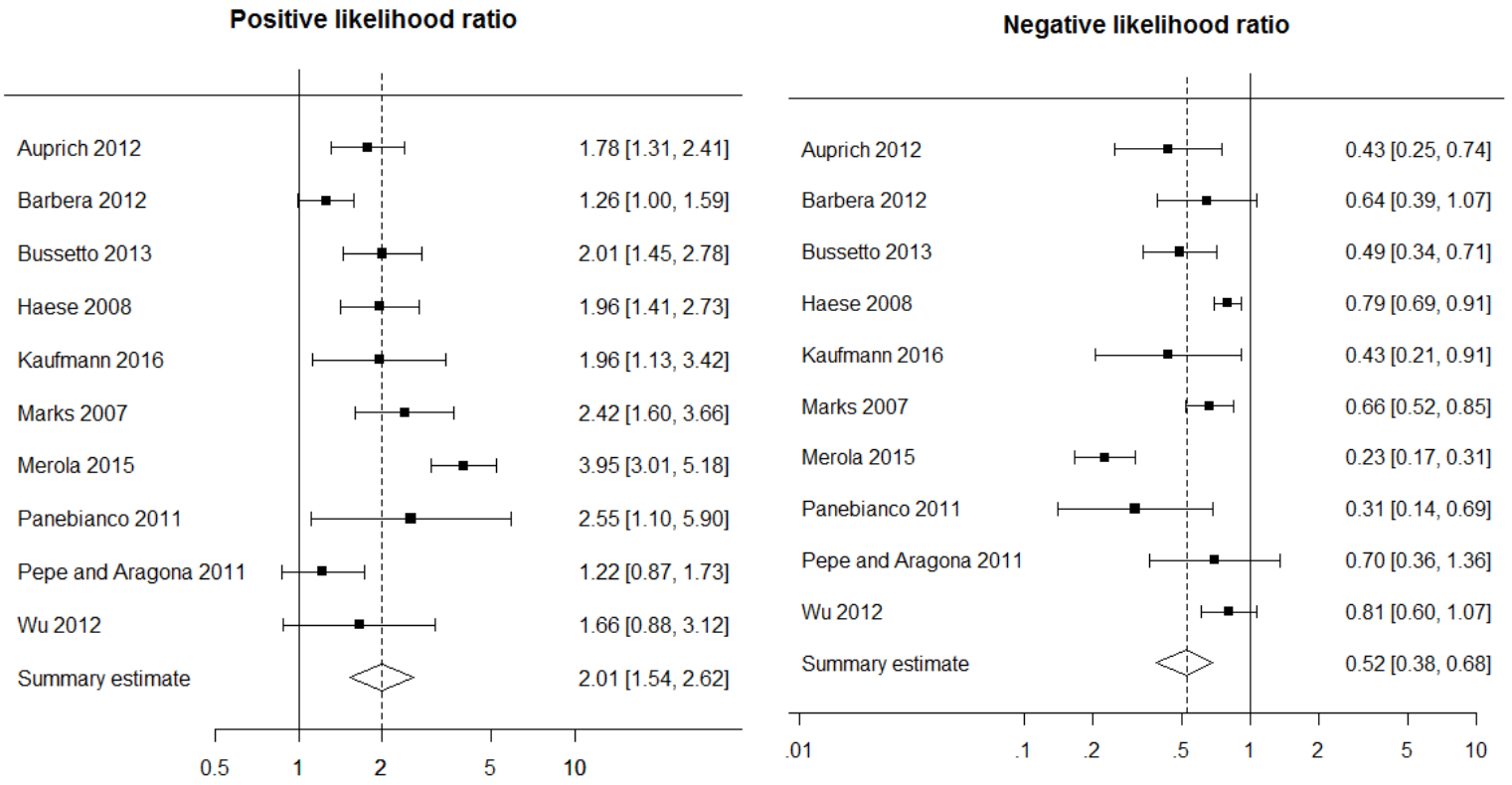
Heterogeneity, sensitivity:

Tau^2 =0.75,Chi^2=91.44, df=9 (p<0.001), I^2 = 90.2%

Heterogeneity, specificity

Tau^2 =0.52,Ch^2=103.27, df=9 (p<0.001), I^2 = 91.3%

Prostate cancer antigen 3 threshold cut off 50 (Reference standard Biopsy) - Positive and Negative likelihood ratios



Heterogeneity, Positive LR:

Tau^2 =0.14,Ch^2=48.98, df=9 (p<0.001), I^2 = 81.6%

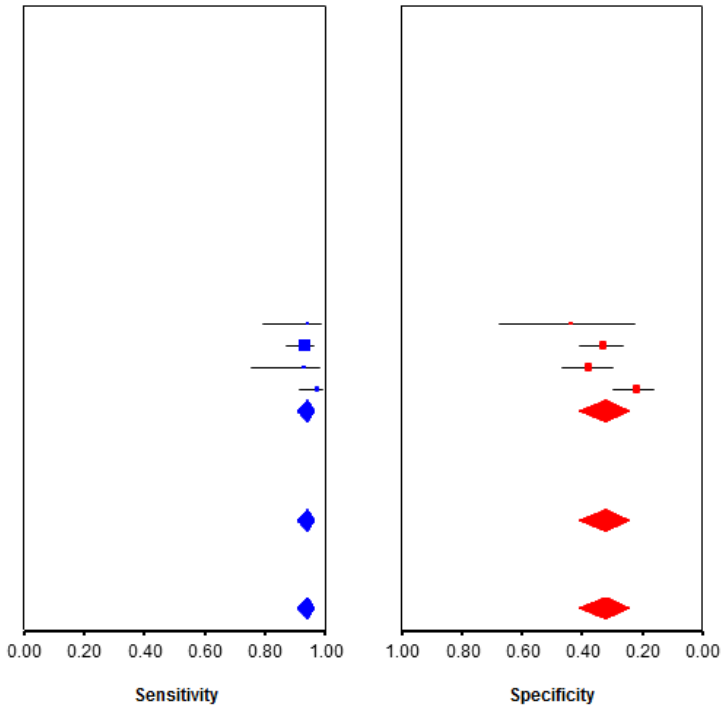
Heterogeneity, Negative LR

Tau^2 =0.17,Chi^2=63.17, df=9 (p<0.001), I^2 = 85.8%

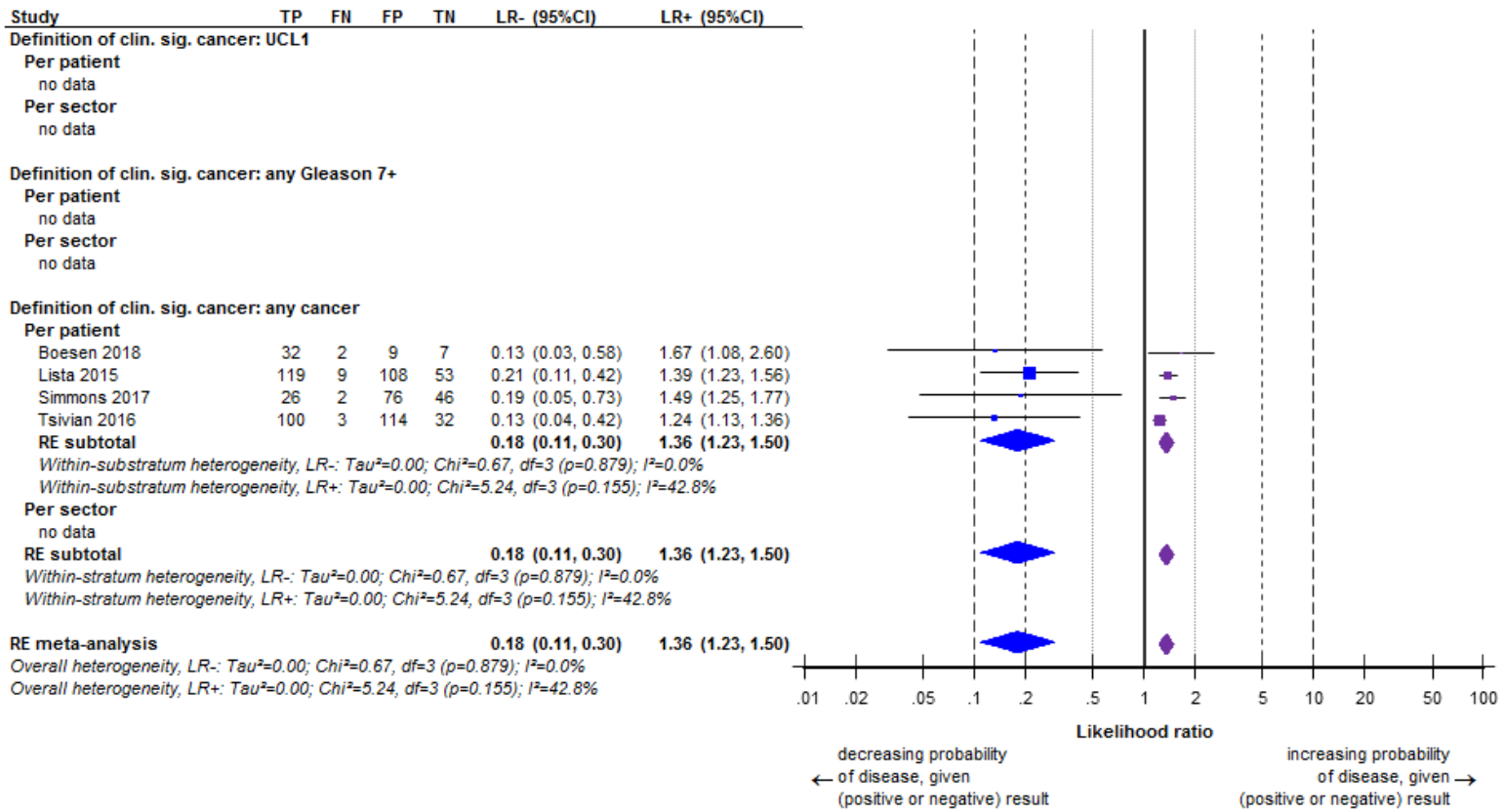
Multiparametric MRI

Multiparametric MRI (score ≥3) sensitivity and specificity Any cancer

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
Boesen 2018	32	2	9	7	0.94 (0.79, 0.99)	0.44 (0.22, 0.68)
Lista 2015	119	9	108	53	0.93 (0.87, 0.96)	0.33 (0.26, 0.41)
Simmons 2017	26	2	76	46	0.93 (0.76, 0.98)	0.38 (0.30, 0.47)
Tsivian 2016	100	3	114	32	0.97 (0.91, 0.99)	0.22 (0.16, 0.29)
RE subtotal					**0.94 (0.91, 0.96)**	**0.32 (0.24, 0.41)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=1.95, df=3 (p=0.582); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=0.10; Chi²=9.49, df=3 (p=0.023); I²=68.4%						
Per sector						
no data						
RE subtotal					**0.94 (0.91, 0.96)**	**0.32 (0.24, 0.41)**
Within-stratum heterogeneity, sens: Tau²=0.00; Chi²=1.95, df=3 (p=0.582); I²=0.0%						
Within-stratum heterogeneity, spec: Tau²=0.10; Chi²=9.49, df=3 (p=0.023); I²=68.4%						
RE meta-analysis					**0.94 (0.91, 0.96)**	**0.32 (0.24, 0.41)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=1.95, df=3 (p=0.582); I²=0.0%						
Overall heterogeneity, spec: Tau²=0.10; Chi²=9.49, df=3 (p=0.023); I²=68.4%						

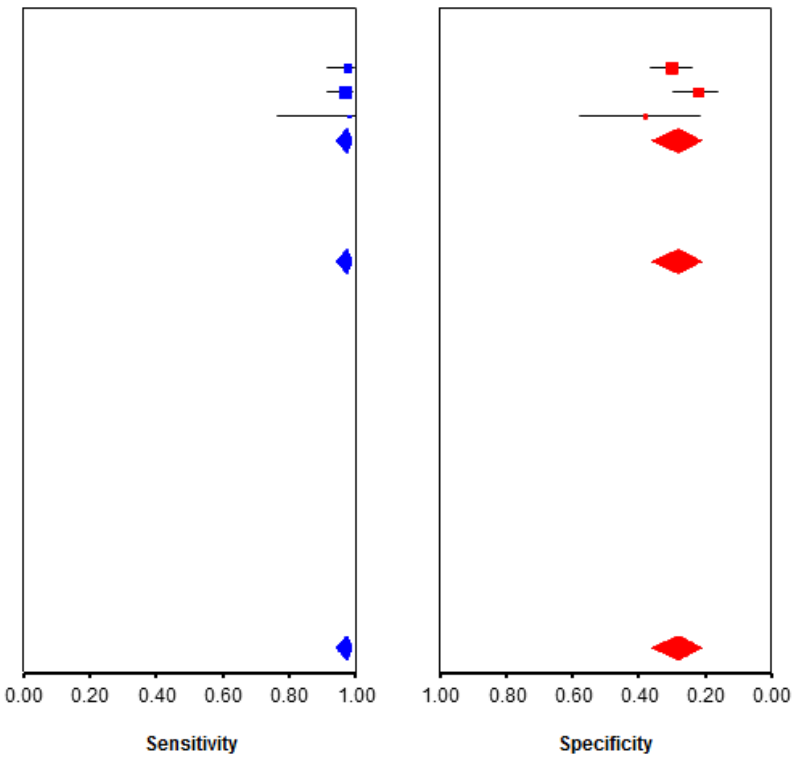


Multiparametric MRI (score ≥3) positive and negative likelihood ratios Any cancer



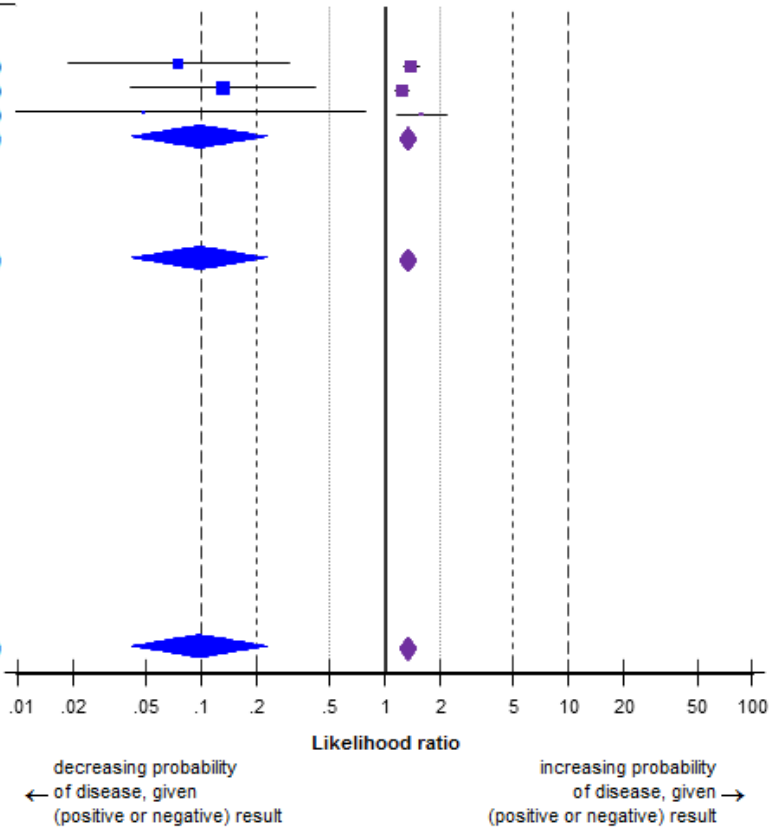
Multiparametric MRI (score ≥3) sensitivity and specificity - clinically significant prostate cancer

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
Boesen 2018	86	2	141	60	0.98 (0.91, 0.99)	0.30 (0.24, 0.37)
Simmons 2017	100	3	114	32	0.97 (0.91, 0.99)	0.22 (0.16, 0.29)
Tsivian 2016	26	0	15	9	0.98 (0.76, 1.00)	0.38 (0.21, 0.58)
RE subtotal					**0.97 (0.94, 0.99)**	**0.28 (0.21, 0.36)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=0.13, df=2 (p=0.935); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=0.05; Chi²=4.18, df=2 (p=0.124); I²=52.1%						
Per sector						
no data						
RE subtotal					**0.97 (0.94, 0.99)**	**0.28 (0.21, 0.36)**
Within-stratum heterogeneity, sens: Tau²=0.00; Chi²=0.13, df=2 (p=0.935); I²=0.0%						
Within-stratum heterogeneity, spec: Tau²=0.05; Chi²=4.18, df=2 (p=0.124); I²=52.1%						
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
no data						
Per sector						
no data						
RE meta-analysis					**0.97 (0.94, 0.99)**	**0.28 (0.21, 0.36)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=0.13, df=2 (p=0.935); I²=0.0%						
Overall heterogeneity, spec: Tau²=0.05; Chi²=4.18, df=2 (p=0.124); I²=52.1%						

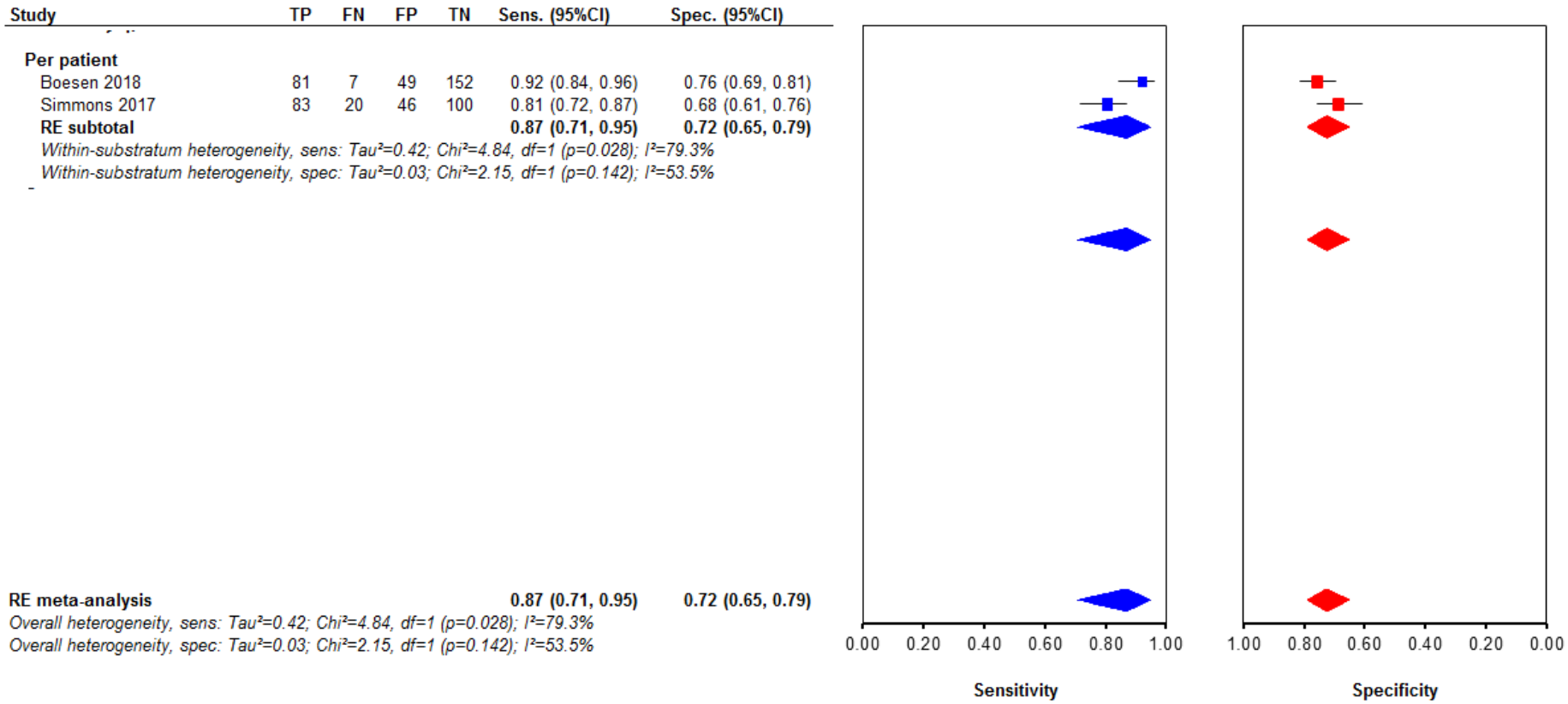


Multiparametric MRI (score ≥3) poitive and negative likelihood ratio clinically significant cancer

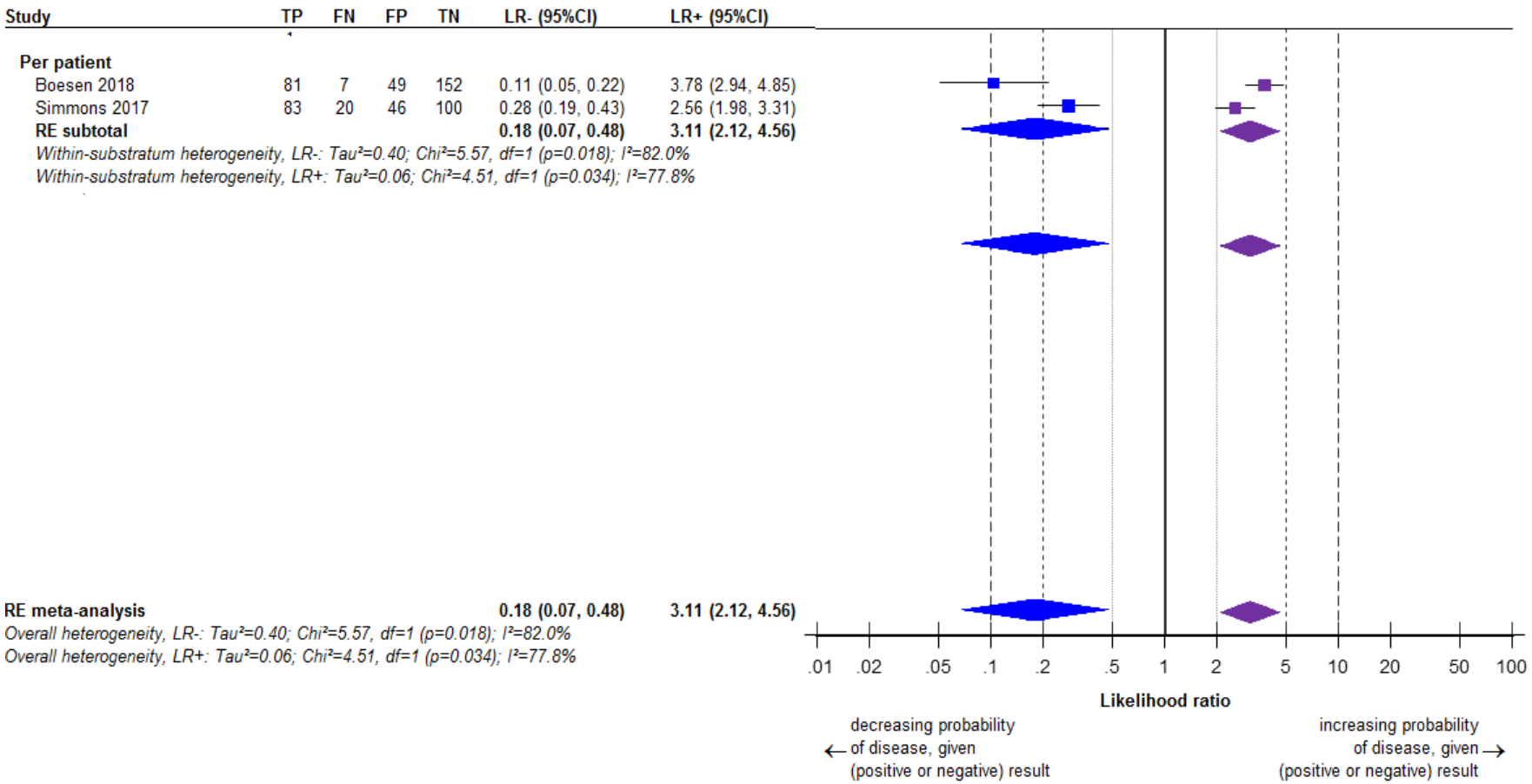
Study	TP	FN	FP	TN	LR- (95%CI)	LR+ (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
Boesen 2018	86	2	141	60	0.08 (0.02, 0.30)	1.39 (1.27, 1.53)
Simmons 2017	100	3	114	32	0.13 (0.04, 0.42)	1.24 (1.13, 1.36)
Tsivian 2016	26	0	15	9	0.05 (0.00, 0.79)	1.58 (1.16, 2.16)
RE subtotal					**0.10 (0.04, 0.23)**	**1.34 (1.20, 1.49)**
Within-substratum heterogeneity, LR-: Tau²=0.00; Chi²=0.63, df=2 (p=0.728); I²=0.0%						
Within-substratum heterogeneity, LR+: Tau²=0.00; Chi²=4.14, df=2 (p=0.126); I²=51.6%						
Per sector						
no data						
RE subtotal					**0.10 (0.04, 0.23)**	**1.34 (1.20, 1.49)**
Within-stratum heterogeneity, LR-: Tau²=0.00; Chi²=0.63, df=2 (p=0.728); I²=0.0%						
Within-stratum heterogeneity, LR+: Tau²=0.00; Chi²=4.14, df=2 (p=0.126); I²=51.6%						
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
no data						
Per sector						
no data						
RE meta-analysis					**0.10 (0.04, 0.23)**	**1.34 (1.20, 1.49)**
Overall heterogeneity, LR-: Tau²=0.00; Chi²=0.63, df=2 (p=0.728); I²=0.0%						
Overall heterogeneity, LR+: Tau²=0.00; Chi²=4.14, df=2 (p=0.126); I²=51.6%						



Multiparametric MRI (score ≥4) sensitivity and specificity - clinically significant cancer



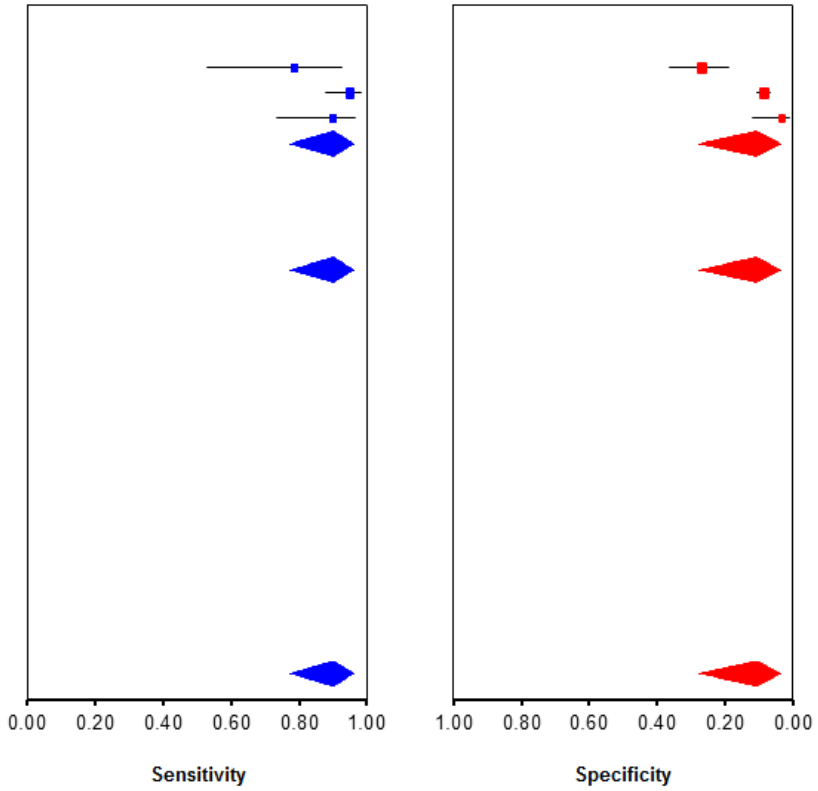
Multiparametric MRI (score ≥4) poitive and negative likelihood ratio – clinically significant cancer



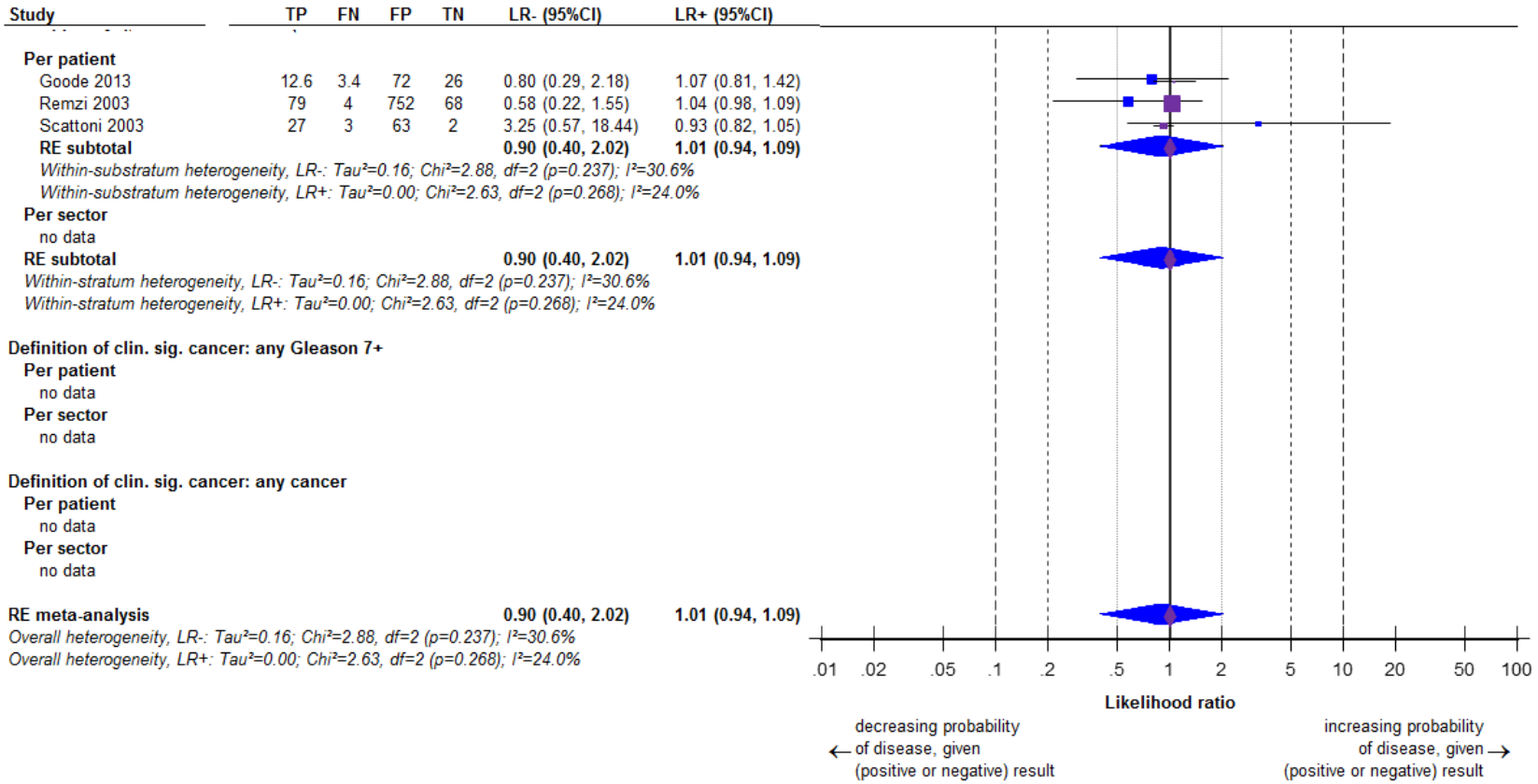
Total prostate specific antigen

Threshold 3.5-4.4ng/ml Sensitivity and Specificty

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Goode 2013	12.6	3.4	72	26	0.79 (0.53, 0.92)	0.27 (0.19, 0.36)
Remzi 2003	79	4	752	68	0.95 (0.88, 0.98)	0.08 (0.07, 0.10)
Scattoni 2003	27	3	63	2	0.90 (0.73, 0.97)	0.03 (0.01, 0.11)
RE subtotal					**0.90 (0.78, 0.96)**	**0.10 (0.03, 0.27)**
Within-substratum heterogeneity, sens: Tau^2=0.40; Chi^2=4.42, df=2 (p=0.110); I^2=54.7%						
Within-substratum heterogeneity, spec: Tau^2=0.91; Chi^2=31.60, df=2 (p<0.001); I^2=93.7%						
Per sector						
no data						
RE subtotal					**0.90 (0.78, 0.96)**	**0.10 (0.03, 0.27)**
Within-stratum heterogeneity, sens: Tau^2=0.40; Chi^2=4.42, df=2 (p=0.110); I^2=54.7%						
Within-stratum heterogeneity, spec: Tau^2=0.91; Chi^2=31.60, df=2 (p<0.001); I^2=93.7%						
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
no data						
Per sector						
no data						
RE meta-analysis					**0.90 (0.78, 0.96)**	**0.10 (0.03, 0.27)**
Overall heterogeneity, sens: Tau^2=0.40; Chi^2=4.42, df=2 (p=0.110); I^2=54.7%						
Overall heterogeneity, spec: Tau^2=0.91; Chi^2=31.60, df=2 (p<0.001); I^2=93.7%						

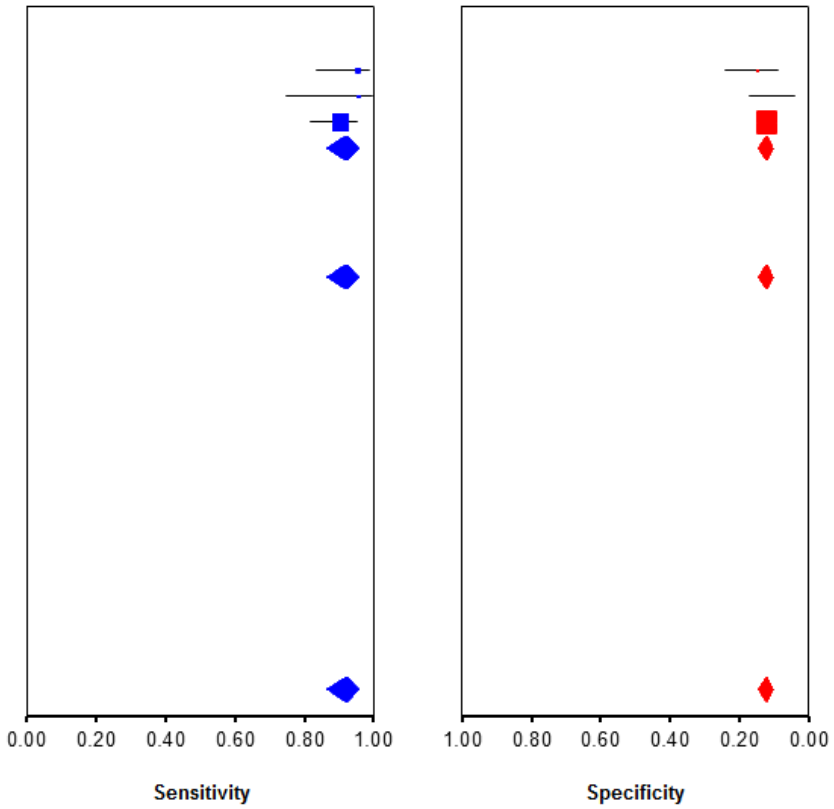


Threshold 3.5-4.4ng/ml Positive and Negative Likelihood ratios

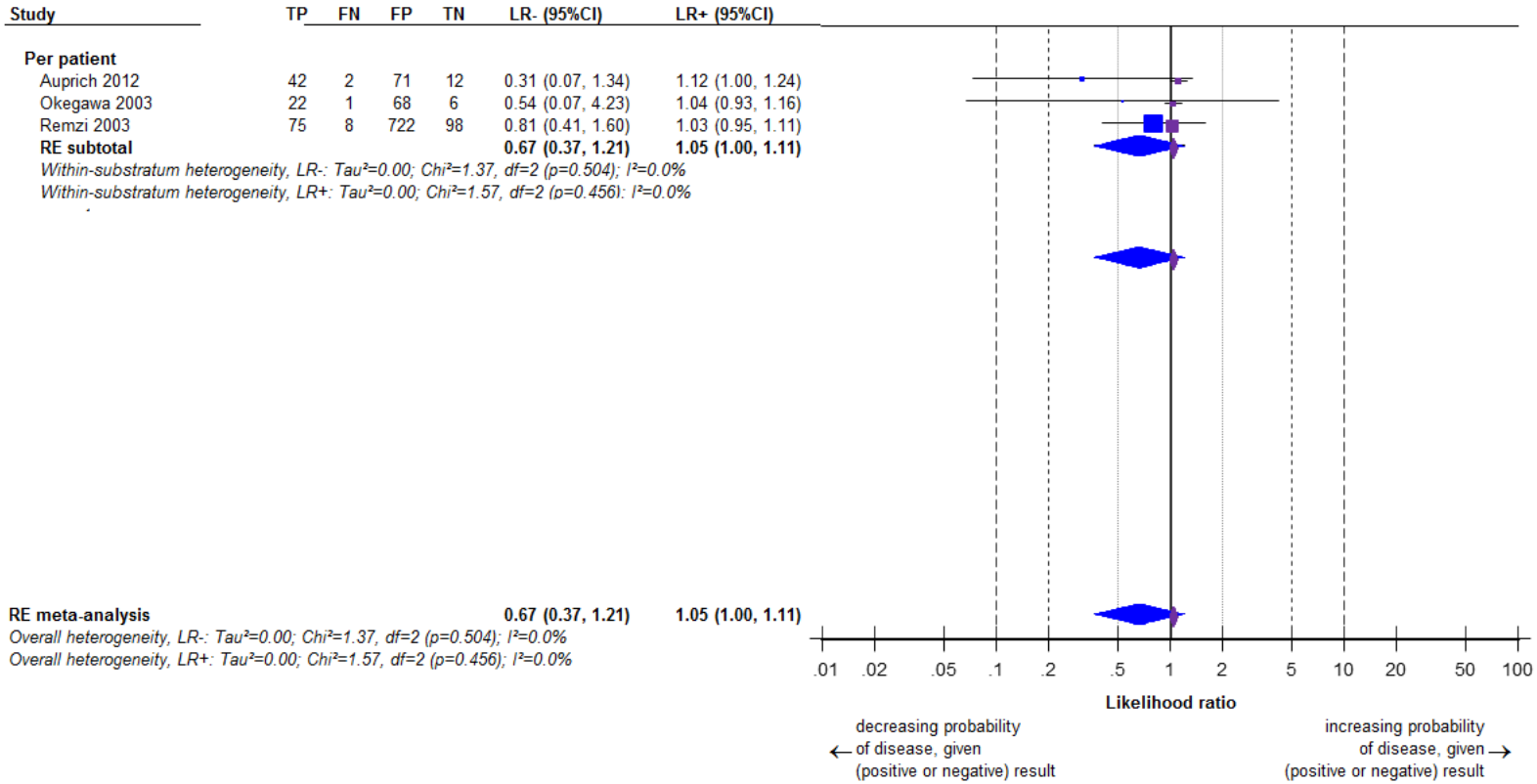


Threshold 4.5-5.4ng/ml Sensitivity and Specificity

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Auprich 2012	42	2	71	12	0.95 (0.84, 0.99)	0.14 (0.08, 0.24)
Okegawa 2003	22	1	68	6	0.96 (0.75, 0.99)	0.08 (0.04, 0.17)
Remzi 2003	75	8	722	98	0.90 (0.82, 0.95)	0.12 (0.10, 0.14)
RE subtotal					**0.92 (0.86, 0.96)**	**0.12 (0.10, 0.14)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=1.39, df=2 (p=0.500); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=0.00; Chi²=1.52, df=2 (p=0.469); I²=0.0%						
RE meta-analysis					**0.92 (0.86, 0.96)**	**0.12 (0.10, 0.14)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=1.39, df=2 (p=0.500); I²=0.0%						
Overall heterogeneity, spec: Tau²=0.00; Chi²=1.52, df=2 (p=0.469); I²=0.0%						

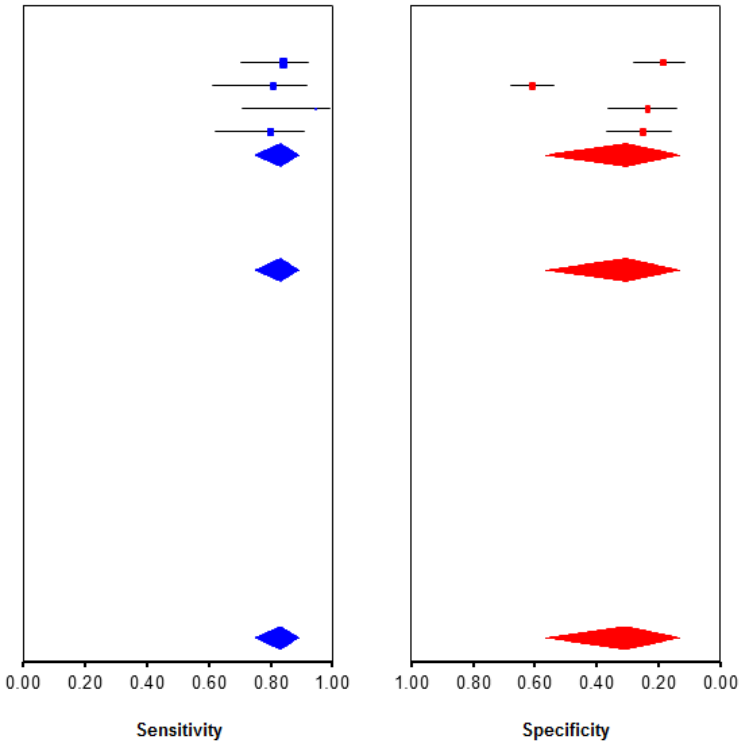


Threshold 4.5-5.4ng/ml Positive and Negative Likelihood ratios

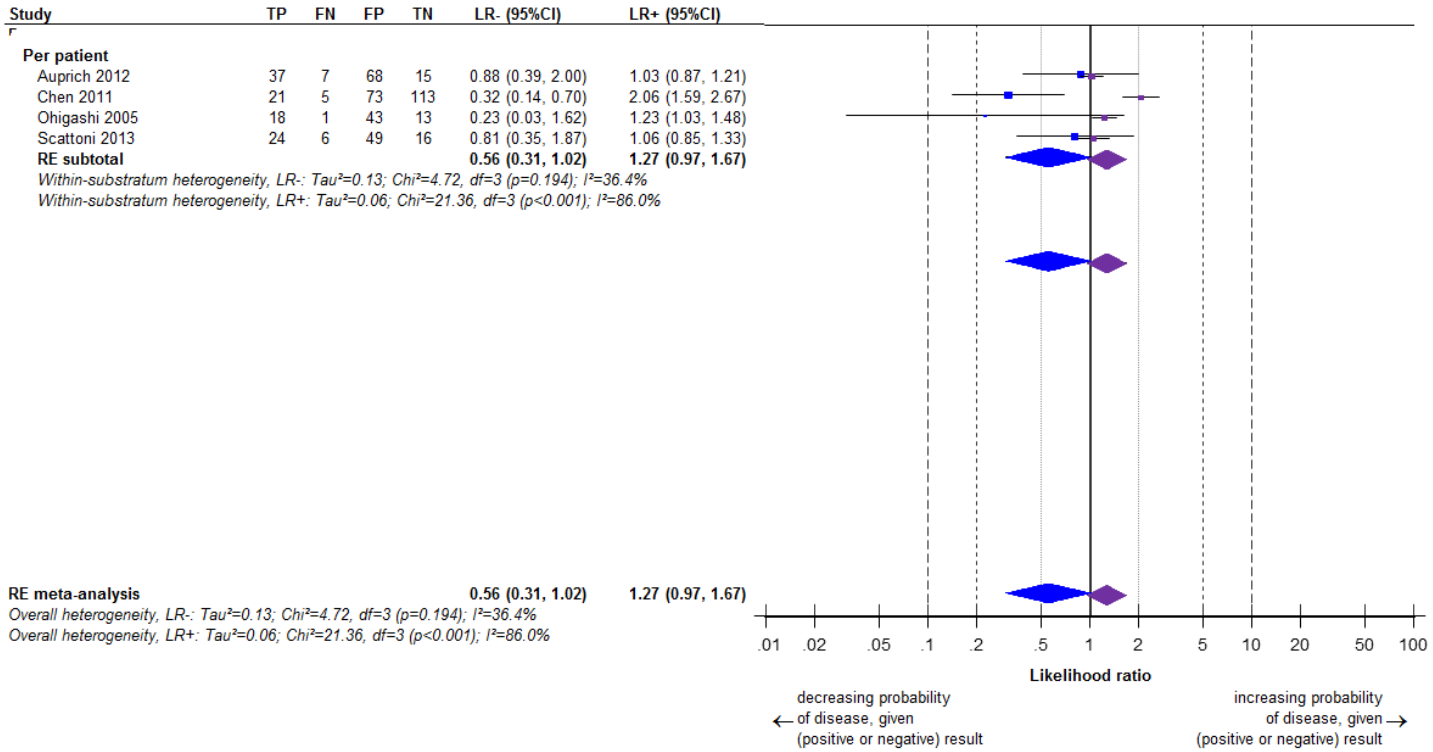


Threshold 5.5 – 6.4ng/ml Sensitivity and Specificty

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Auprich 2012	37	7	68	15	0.84 (0.70, 0.92)	0.18 (0.11, 0.28)
Chen 2011	21	5	73	113	0.81 (0.61, 0.92)	0.61 (0.54, 0.68)
Ohigashi 2005	18	1	43	13	0.95 (0.71, 0.99)	0.23 (0.14, 0.36)
Scattoni 2013	24	6	49	16	0.80 (0.62, 0.91)	0.25 (0.16, 0.36)
RE subtotal					**0.83 (0.75, 0.89)**	**0.30 (0.13, 0.56)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=1.93, df=3 (p=0.587); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=1.14; Chi²=58.22, df=3 (p<0.001); I²=94.8%						
RE meta-analysis					**0.83 (0.75, 0.89)**	**0.30 (0.13, 0.56)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=1.93, df=3 (p=0.587); I²=0.0%						
Overall heterogeneity, spec: Tau²=1.14; Chi²=58.22, df=3 (p<0.001); I²=94.8%						

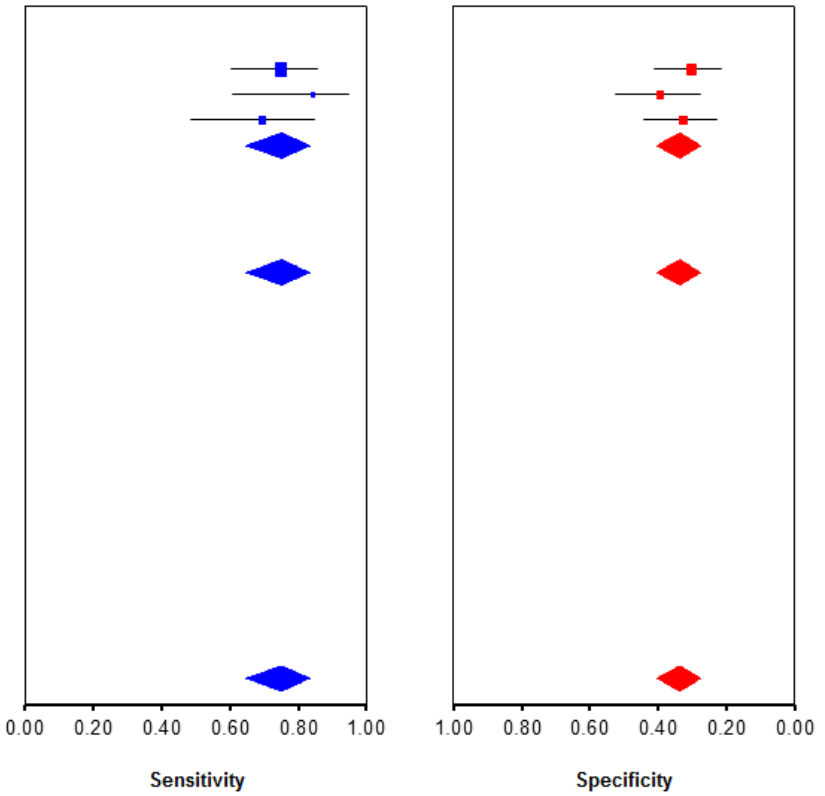


Threshold 5.5 – 6.4ng/ml Likelihood ratios

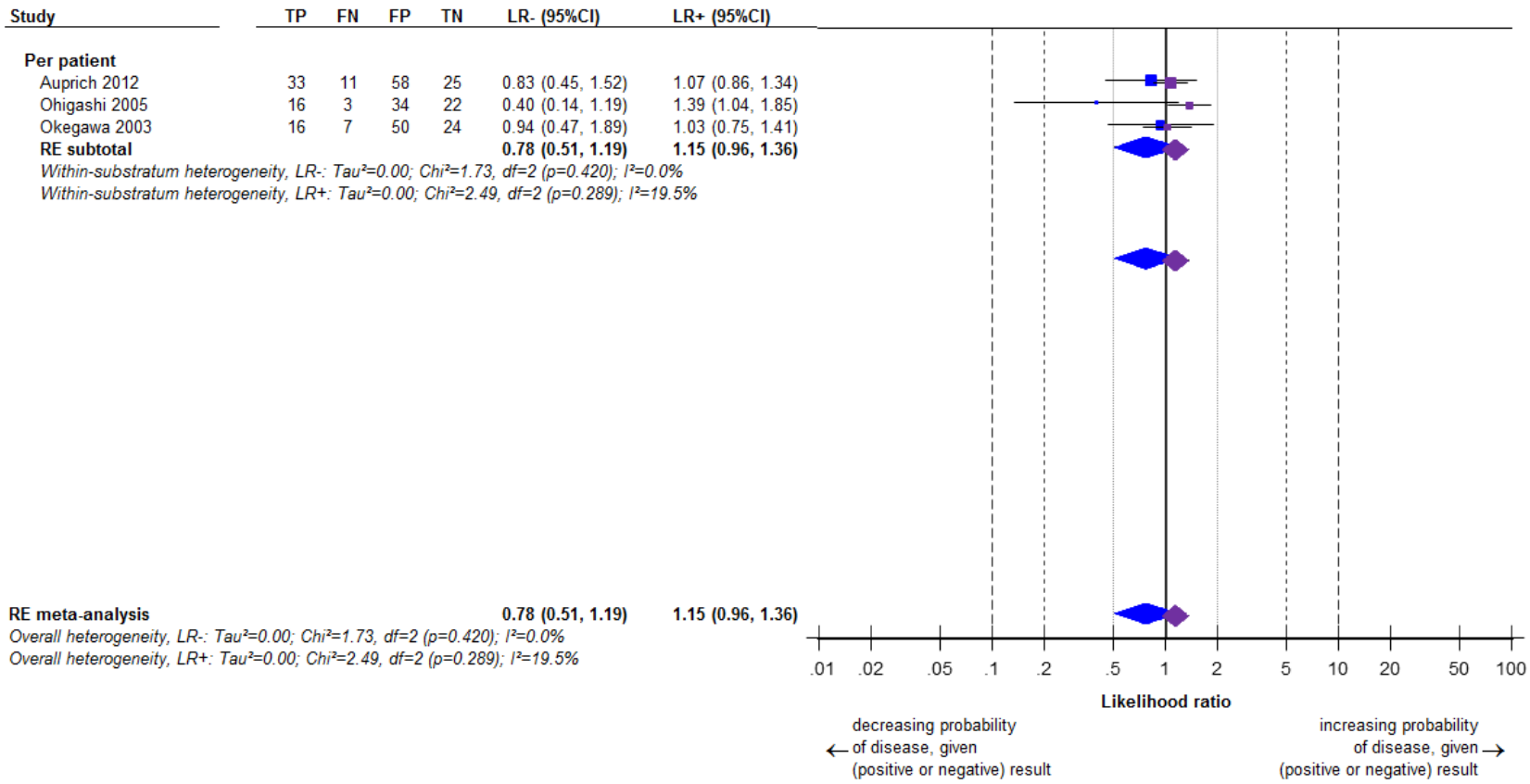


Threshold 6.5 -7.4ng/ml Sensitivity and Specificity

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Auprich 2012	33	11	58	25	0.75 (0.60, 0.86)	0.30 (0.21, 0.41)
Ohigashi 2005	16	3	34	22	0.84 (0.61, 0.95)	0.39 (0.27, 0.53)
Okegawa 2003	16	7	50	24	0.70 (0.48, 0.85)	0.32 (0.23, 0.44)
RE subtotal					**0.75 (0.65, 0.83)**	**0.33 (0.27, 0.40)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=1.20, df=2 (p=0.550); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=0.00; Chi²=1.30, df=2 (p=0.522); I²=0.0%						
RE meta-analysis					**0.75 (0.65, 0.83)**	**0.33 (0.27, 0.40)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=1.20, df=2 (p=0.550); I²=0.0%						
Overall heterogeneity, spec: Tau²=0.00; Chi²=1.30, df=2 (p=0.522); I²=0.0%						

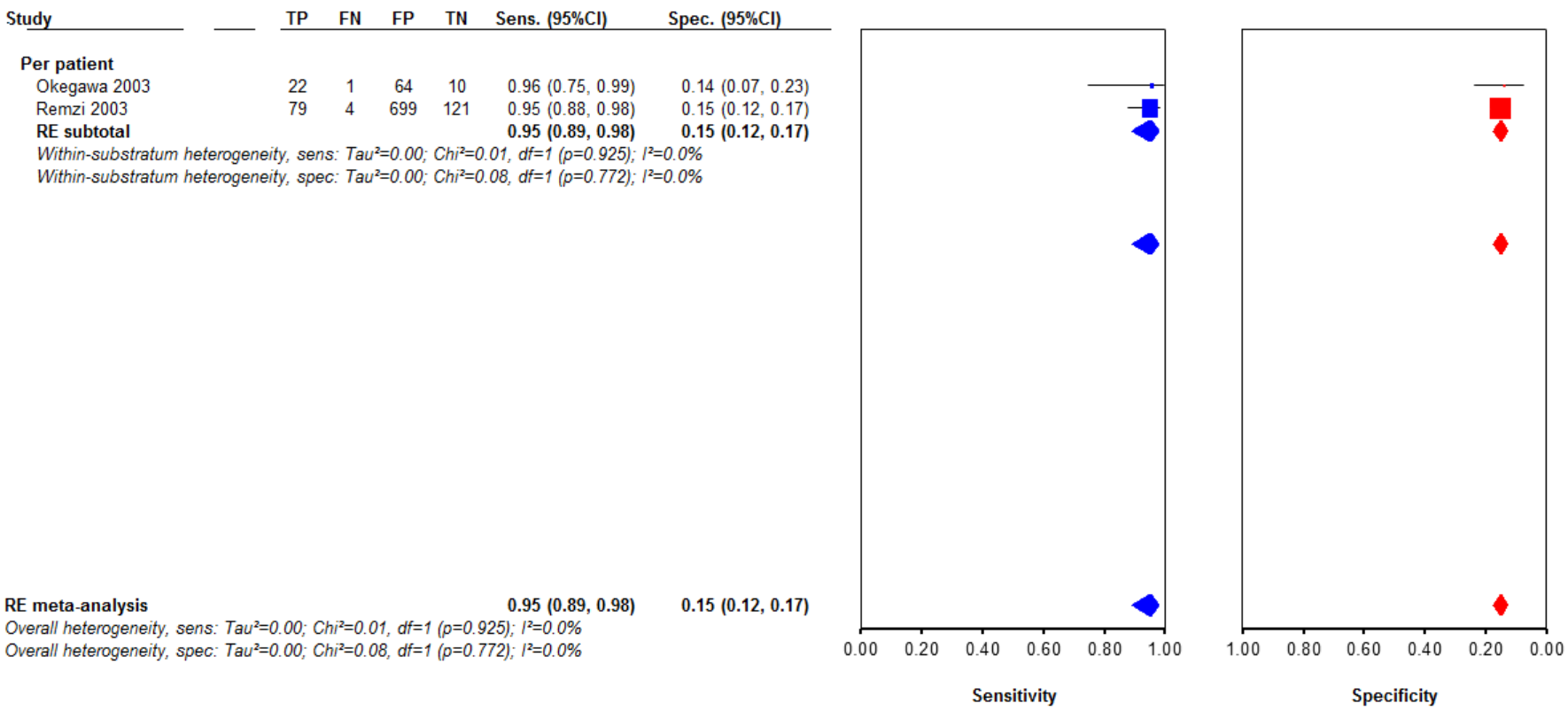


Threshold 6.5 -7.4ng/ml Likelihood ratios

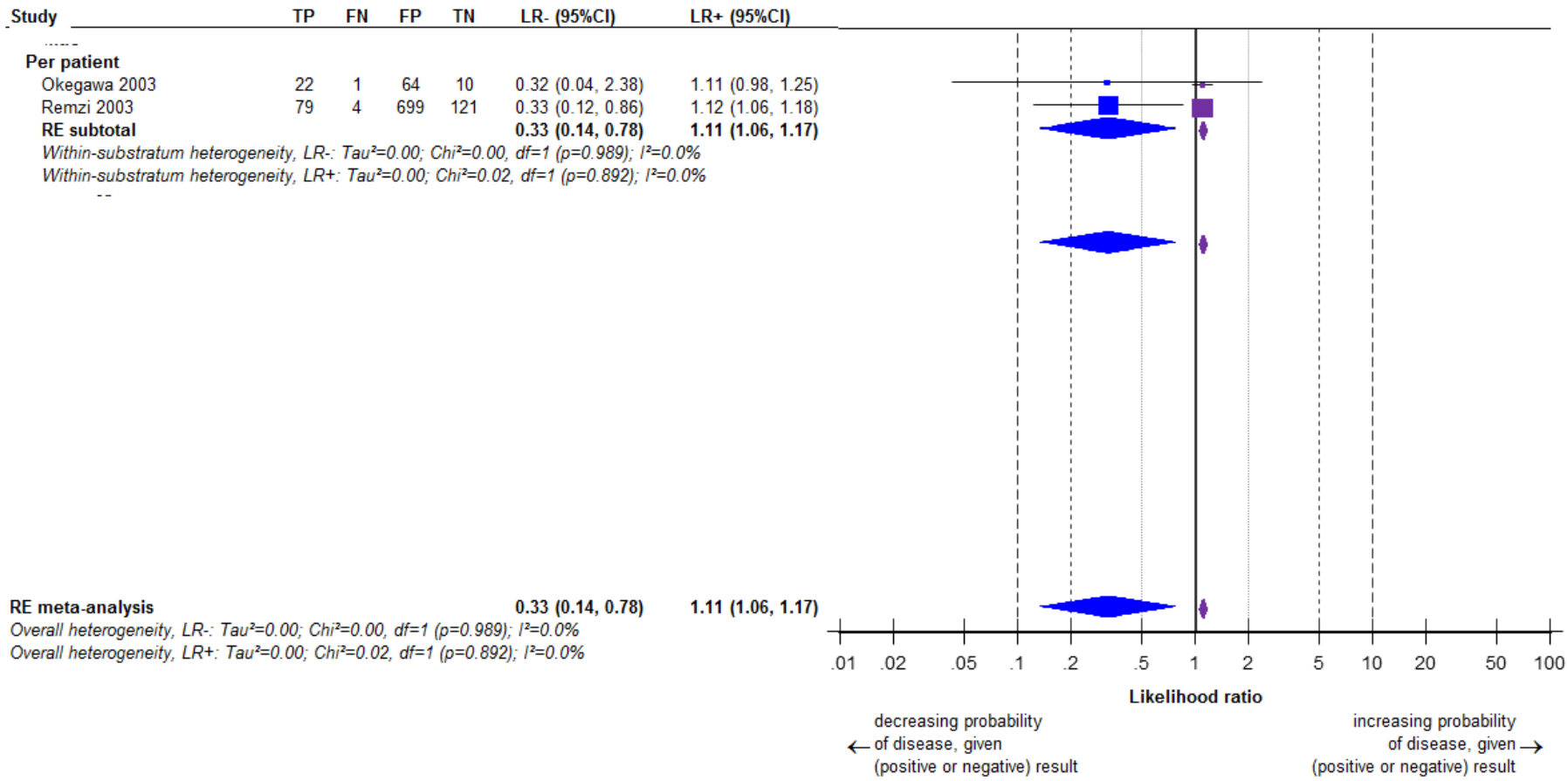


Prostate specific antigen Density

Threshold 0.10ng/ml/ml sensitivity and specificity

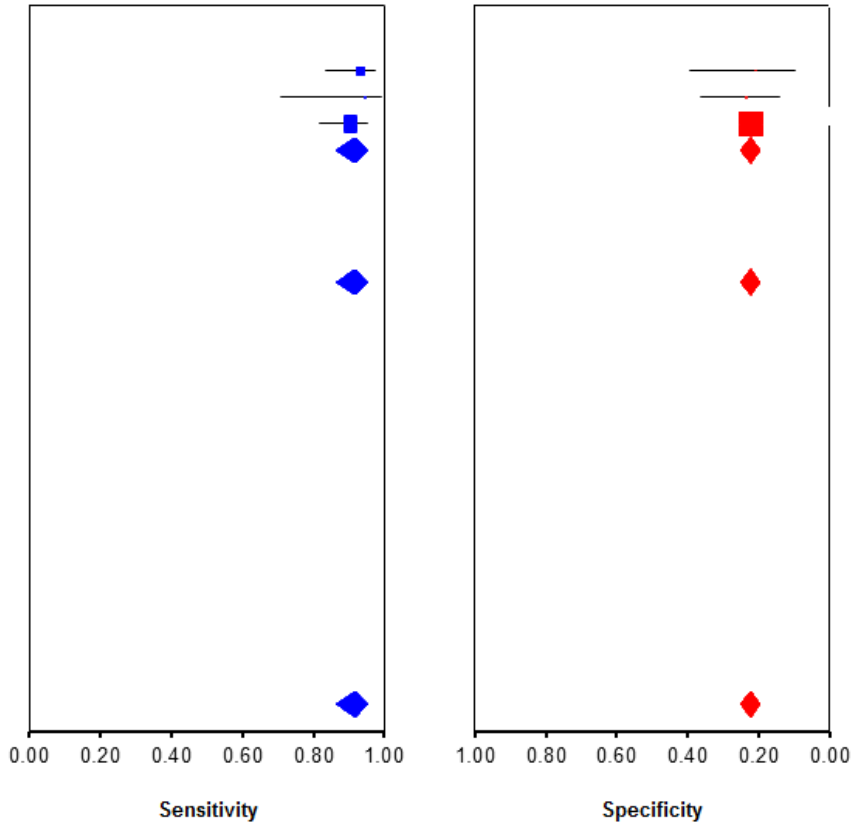


Threshold 10ng/ml/ml positive and negative likelihood ratios

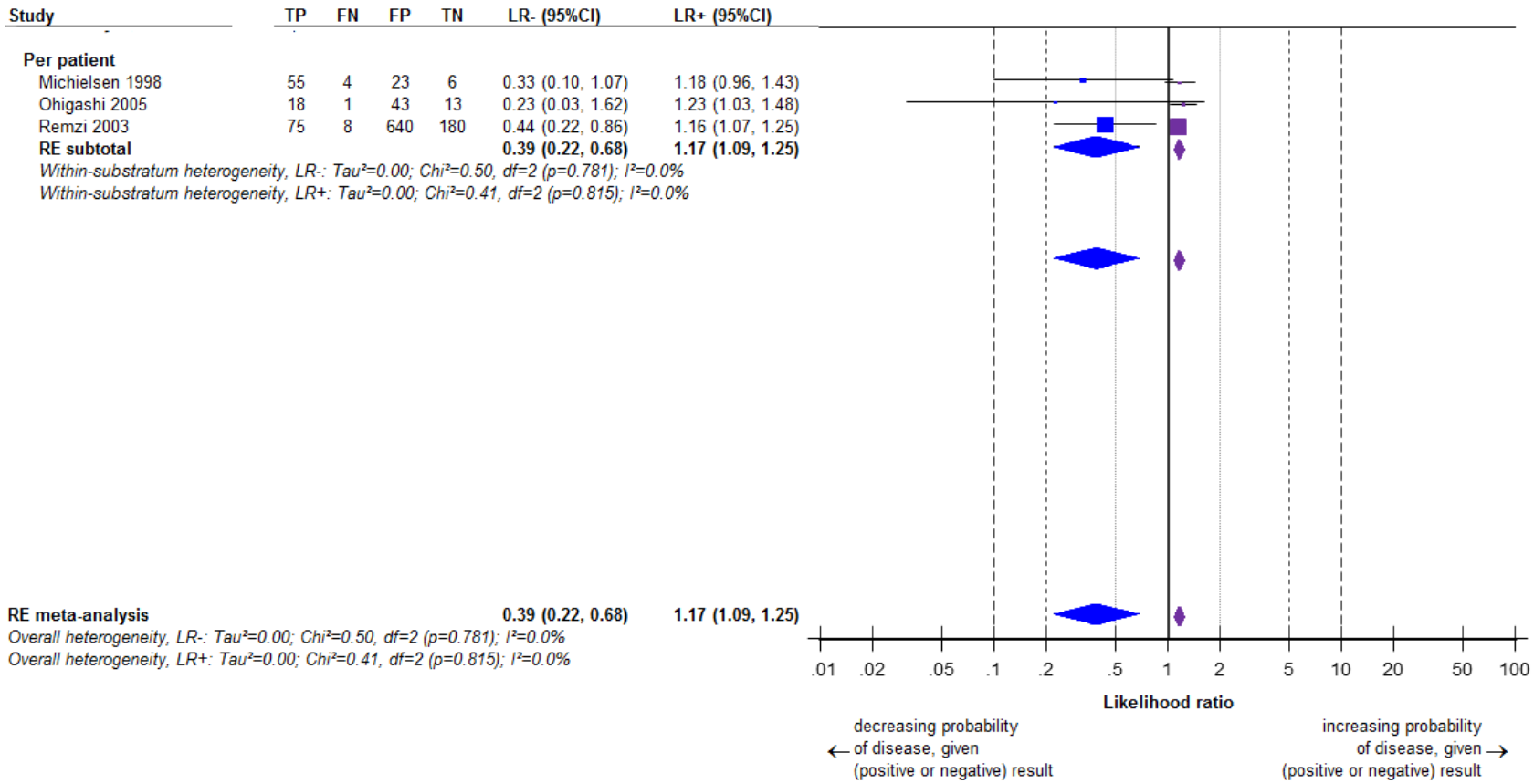


Threshold ≥0.10ng/ml/ml sensitivity and specificity

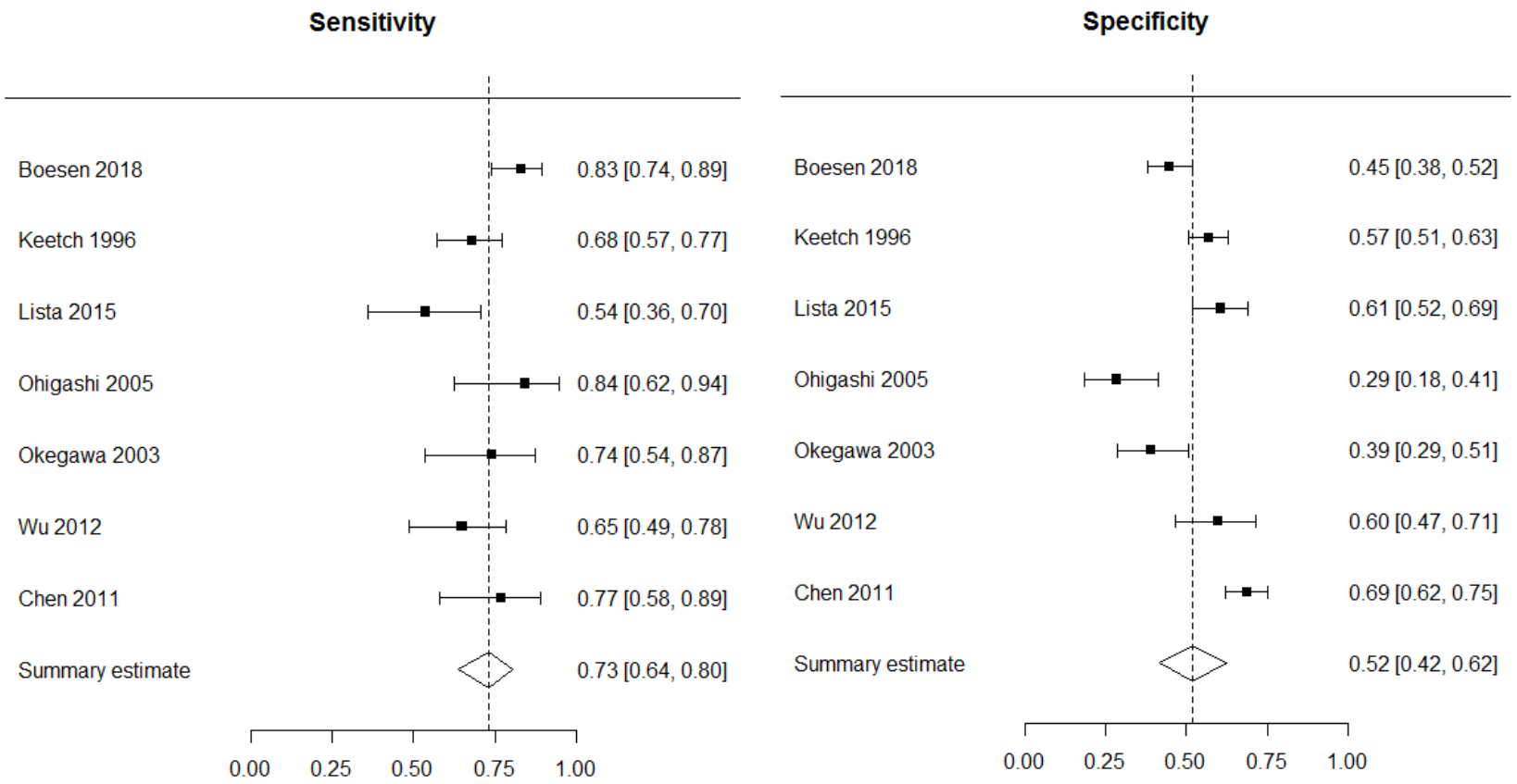
Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Michielsen 1998	55	4	23	6	0.93 (0.83, 0.97)	0.21 (0.10, 0.39)
Ohigashi 2005	18	1	43	13	0.95 (0.71, 0.99)	0.23 (0.14, 0.36)
Remzi 2003	75	8	640	180	0.90 (0.82, 0.95)	0.22 (0.19, 0.25)
RE subtotal					**0.92 (0.86, 0.95)**	**0.22 (0.19, 0.25)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=0.60, df=2 (p=0.741); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=0.00; Chi²=0.08, df=2 (p=0.962); I²=0.0%						
RE meta-analysis					**0.92 (0.86, 0.95)**	**0.22 (0.19, 0.25)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=0.60, df=2 (p=0.741); I²=0.0%						
Overall heterogeneity, spec: Tau²=0.00; Chi²=0.08, df=2 (p=0.962); I²=0.0%						



Threshold ≥0.10ng/ml/ml positive and negative likelihood ratios

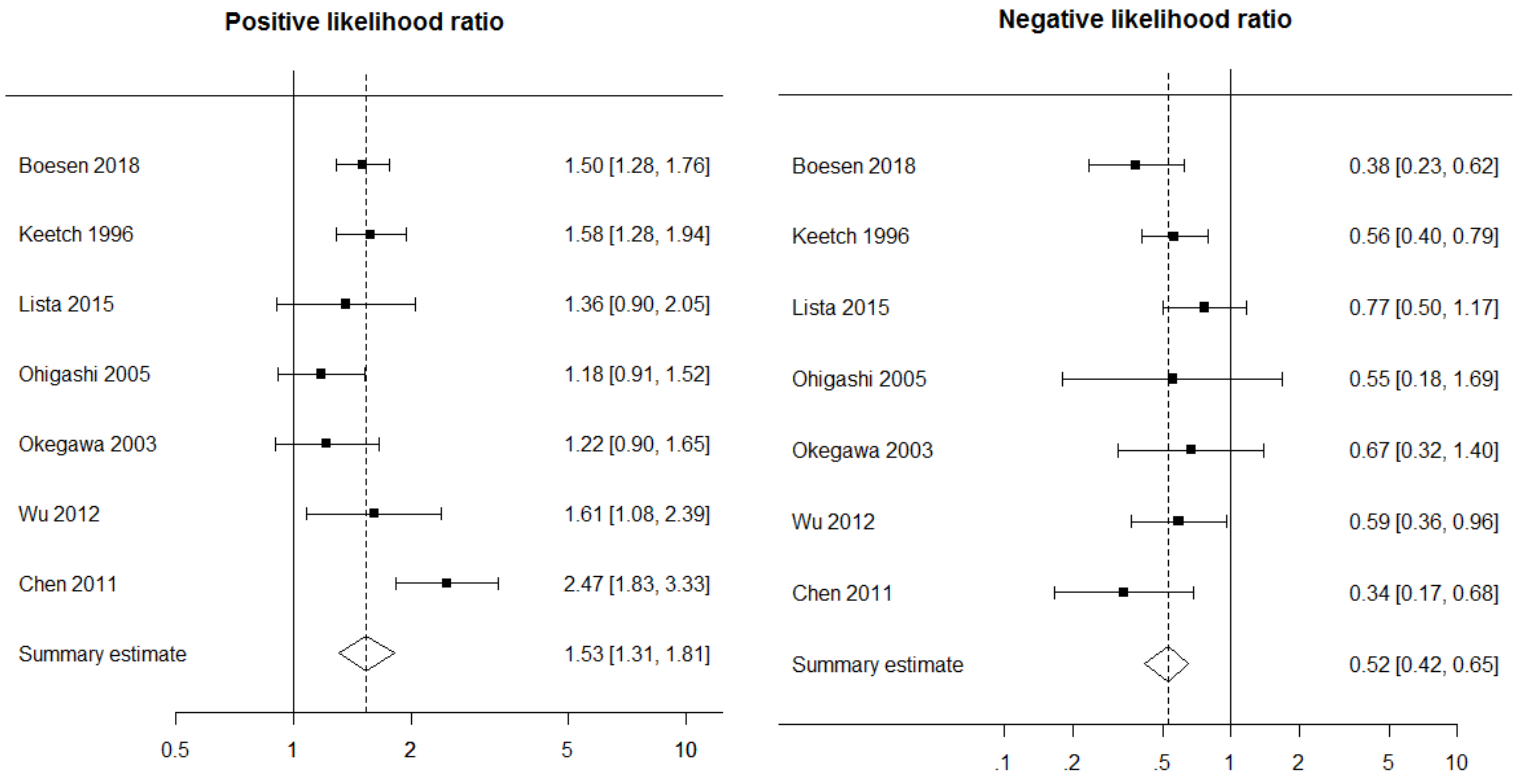


Threshold ≥15ng/ml/ml sensitivity and specificity



Overall heterogeneity, sens: Tau^2=0.15; Chi^2=12.83, df=6 (p=0.046); I^2=53.2%
Overall heterogeneity, spec: Tau^2=0.22; Chi^2=46.01, df=6 (p<0.001); I^2=87.0%

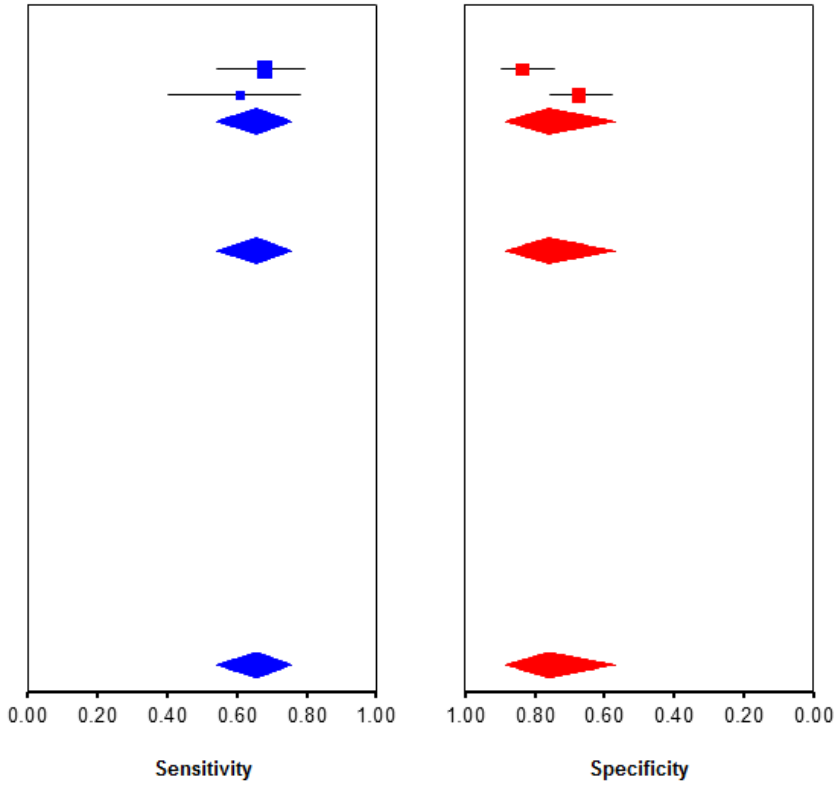
Threshold ≥15ng/ml/cm^3 Negative and likelihood ratio



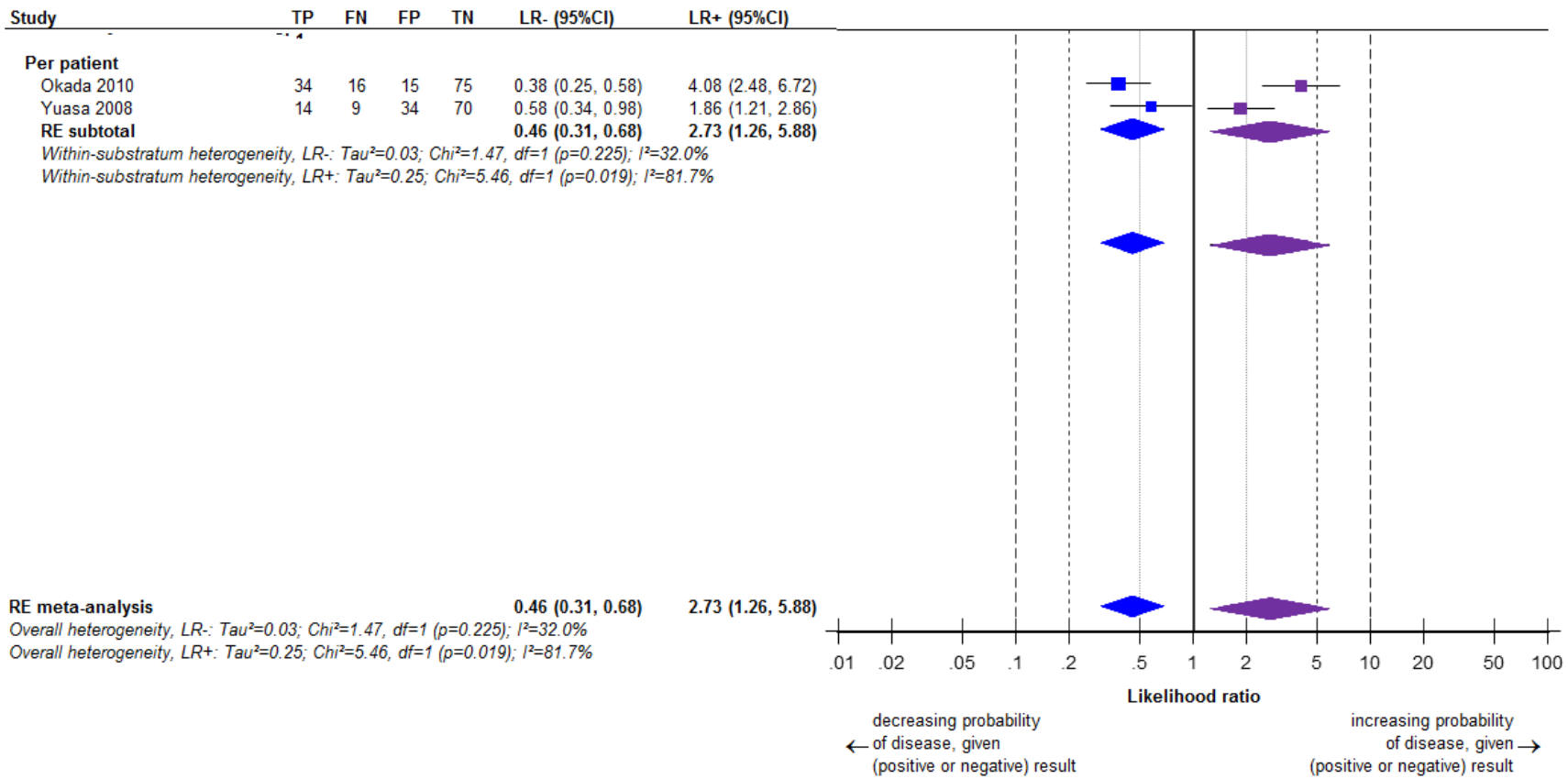
Overall heterogeneity, LR-: Tau²=0.01; Chi²=6.77, df=6 (p=0.342); I²=11.4%
Overall heterogeneity, LR+: Tau²=0.03; Chi²=16.36, df=6 (p=0.012); I²=63.3%

Threshold ≥30ng/ml/cm^3 sensitivity and specificity

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Okada 2010	34	16	15	75	0.68 (0.54, 0.79)	0.83 (0.74, 0.90)
Yuasa 2008	14	9	34	70	0.61 (0.40, 0.78)	0.67 (0.58, 0.76)
RE subtotal					**0.66 (0.54, 0.76)**	**0.76 (0.57, 0.88)**
Within-substratum heterogeneity, sens: Tau²=0.00; Chi²=0.35, df=1 (p=0.552); I²=0.0%						
Within-substratum heterogeneity, spec: Tau²=0.33; Chi²=6.36, df=1 (p=0.012); I²=84.3%						
RE meta-analysis					**0.66 (0.54, 0.76)**	**0.76 (0.57, 0.88)**
Overall heterogeneity, sens: Tau²=0.00; Chi²=0.35, df=1 (p=0.552); I²=0.0%						
Overall heterogeneity, spec: Tau²=0.33; Chi²=6.36, df=1 (p=0.012); I²=84.3%						

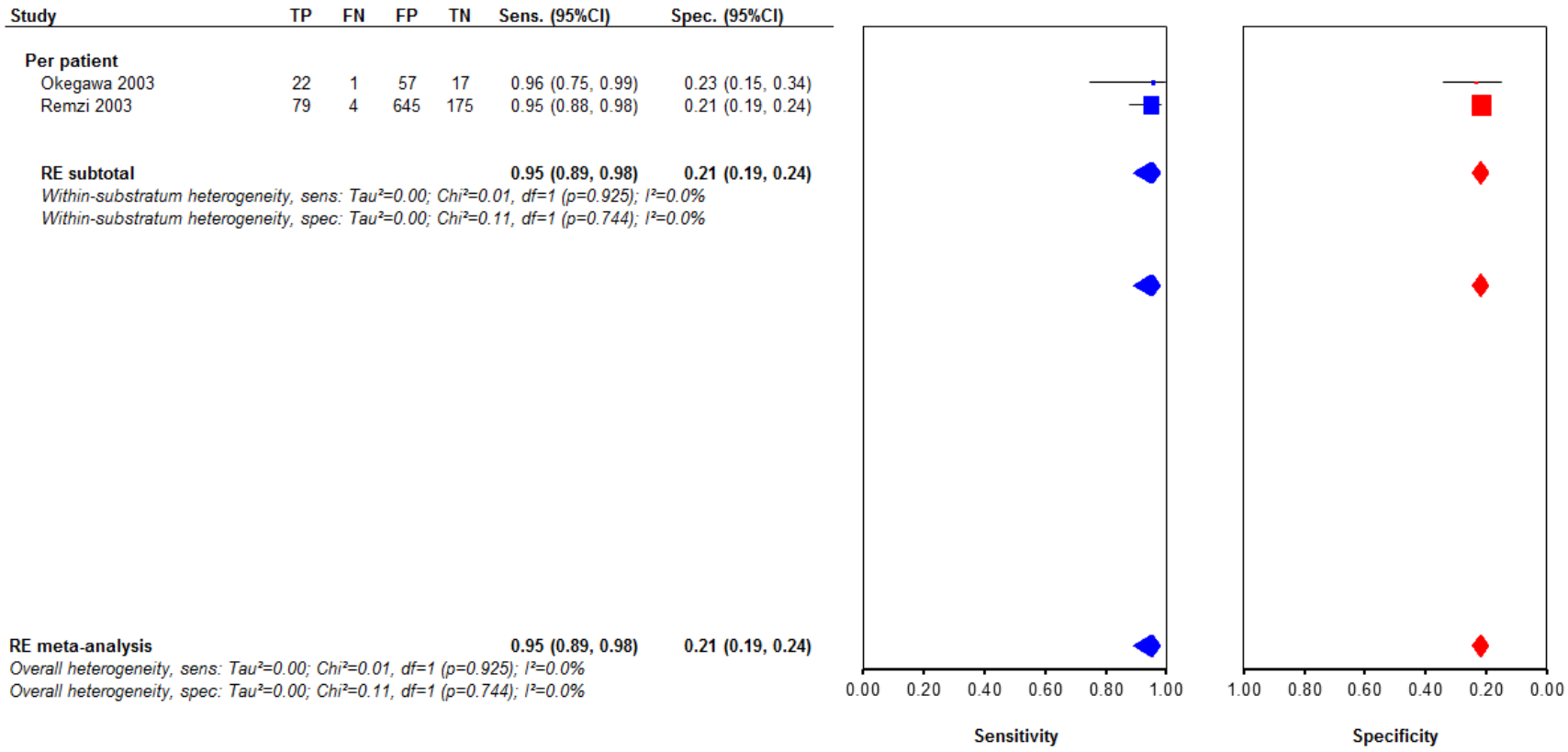


Threshold ≥30ng/ml/ml negative and positive likelihood ratio

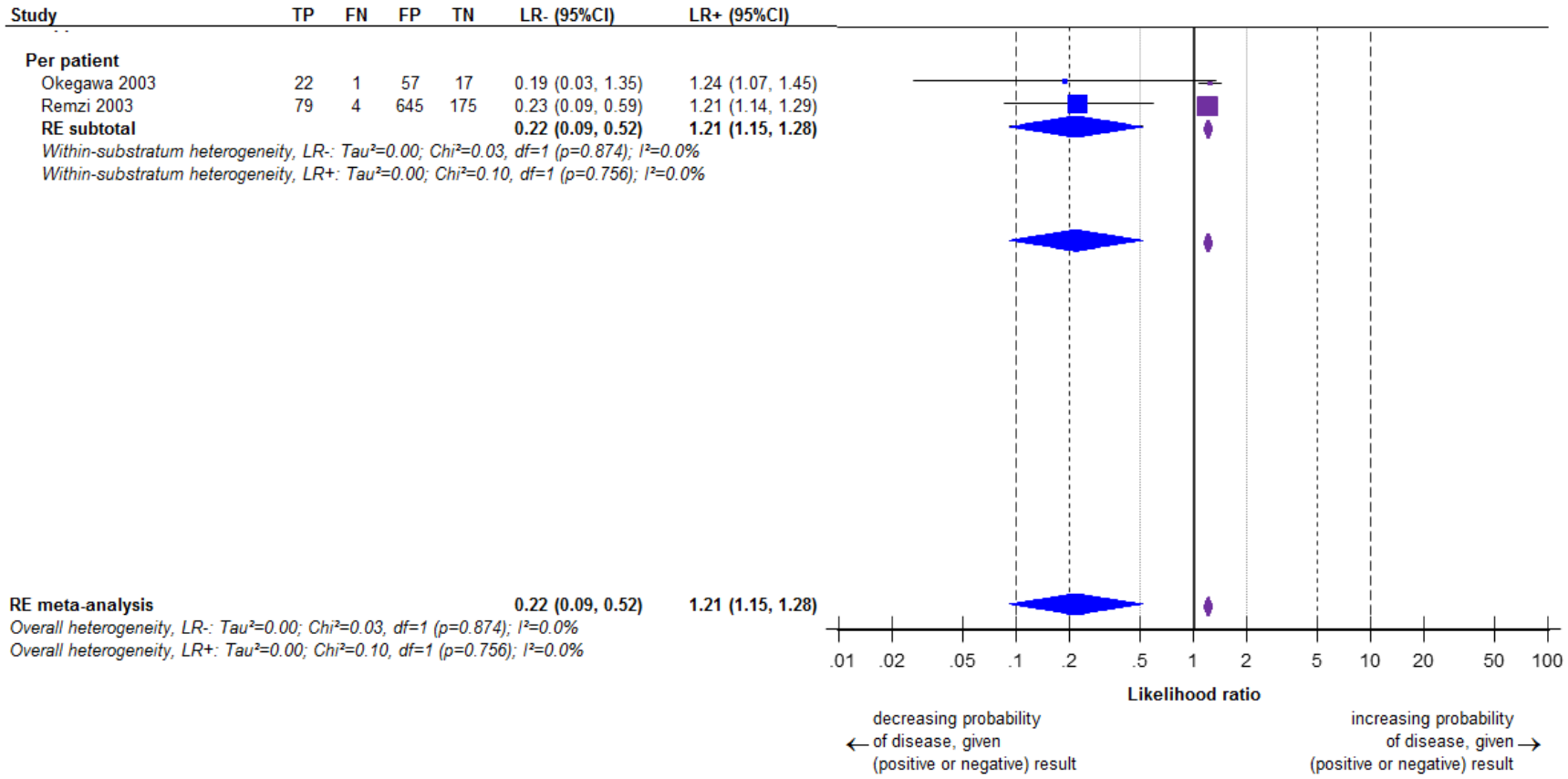


Prostate specific antigen density of the transition zone

Threshold <0.20ng/ml/ml sensitivity and specificity

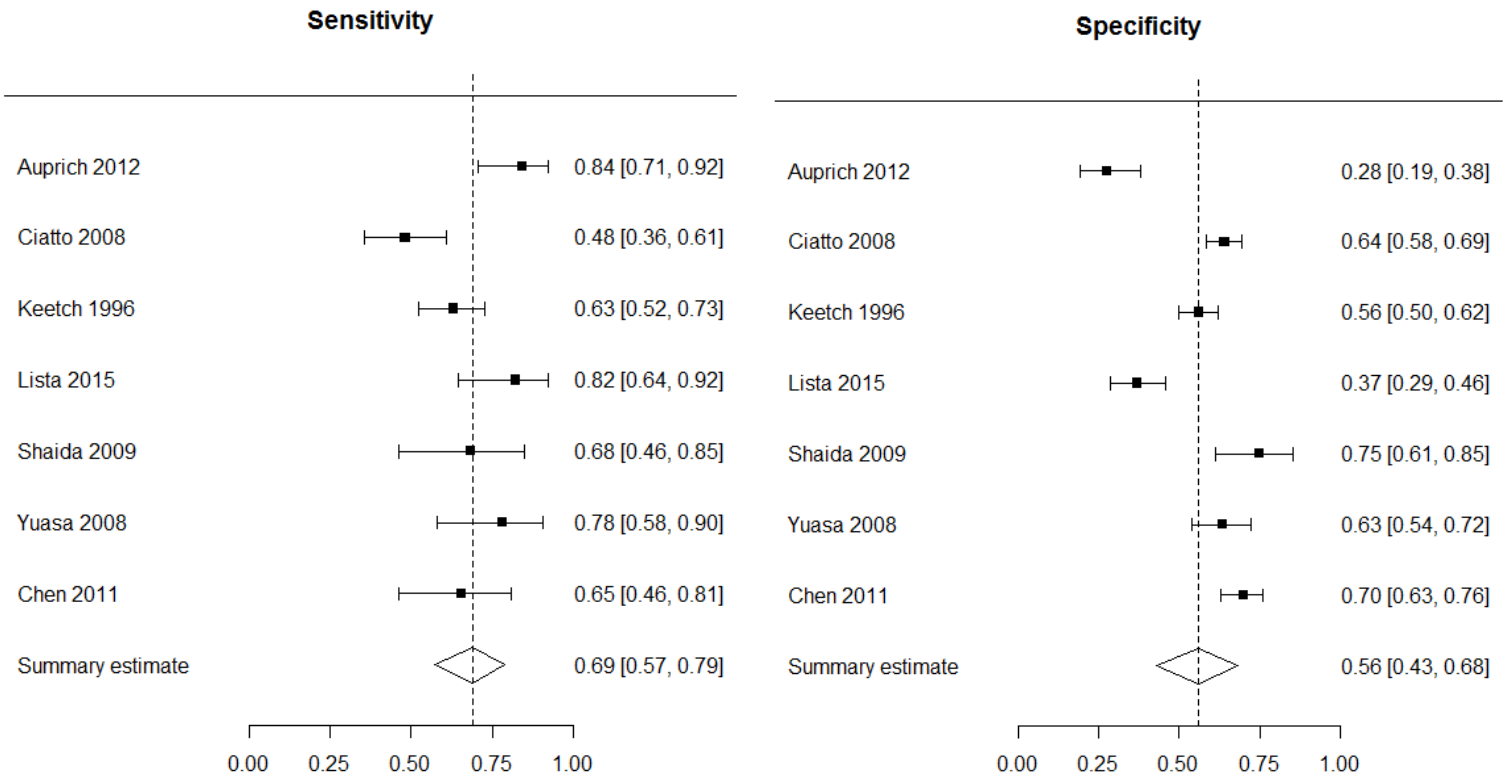


Threshold <0.20ng/mlml positive and negative likelihood ratio



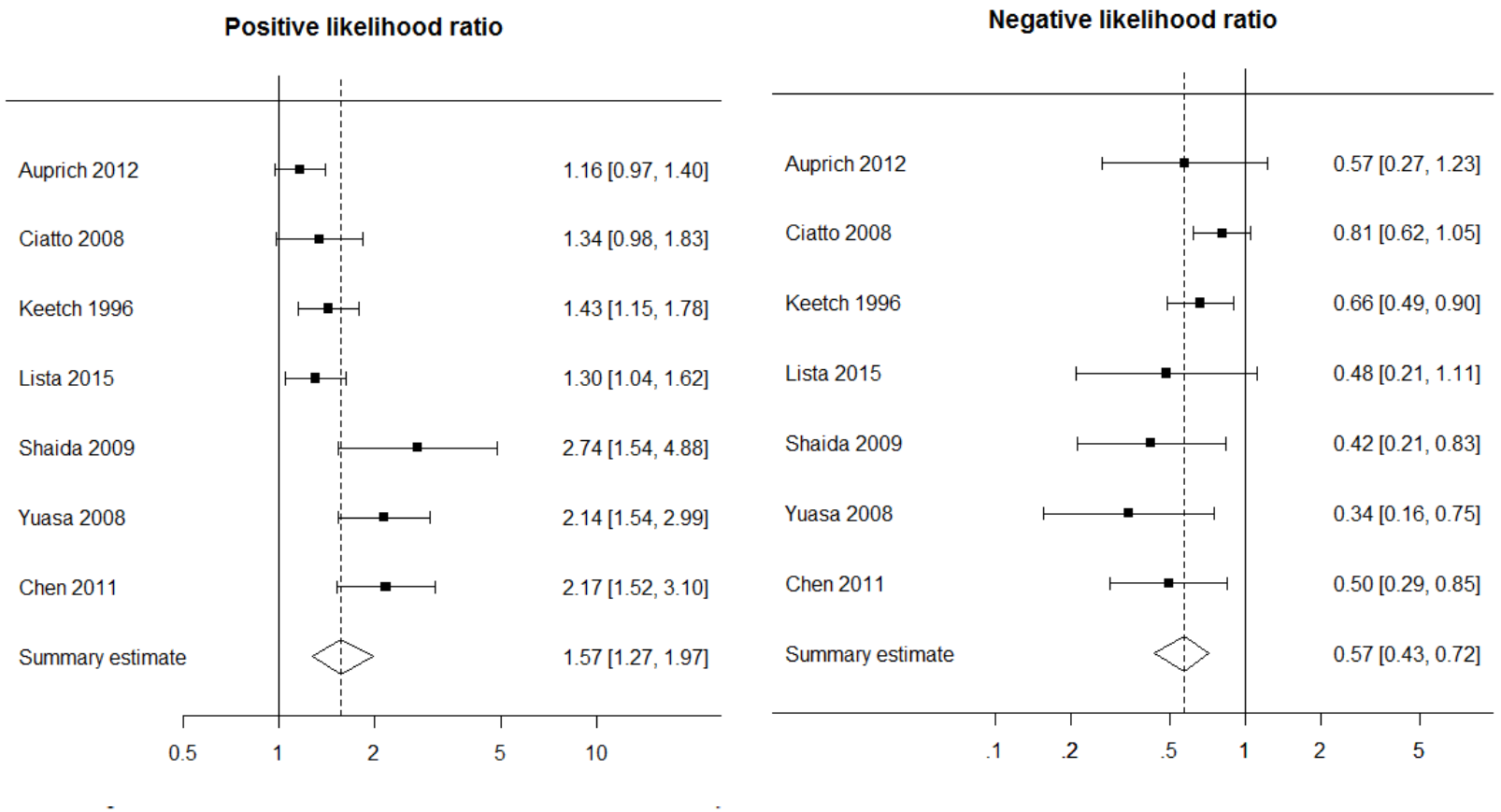
Prostate specific antigen velocity

Threshold 0.75 ng/ml/year - sensitivity and specificity



Overall heterogeneity, sens: Tau^2=0.28; Chi^2=18.38, df=6 (p=0.005); I^2=67.4%
Overall heterogeneity, spec: Tau^2=0.23; Chi^2=52.41, df=6 (p<0.001); I^2=88.6%

Threshold 0.75 ng/ml/year - Positive and Negative likelihood ratios

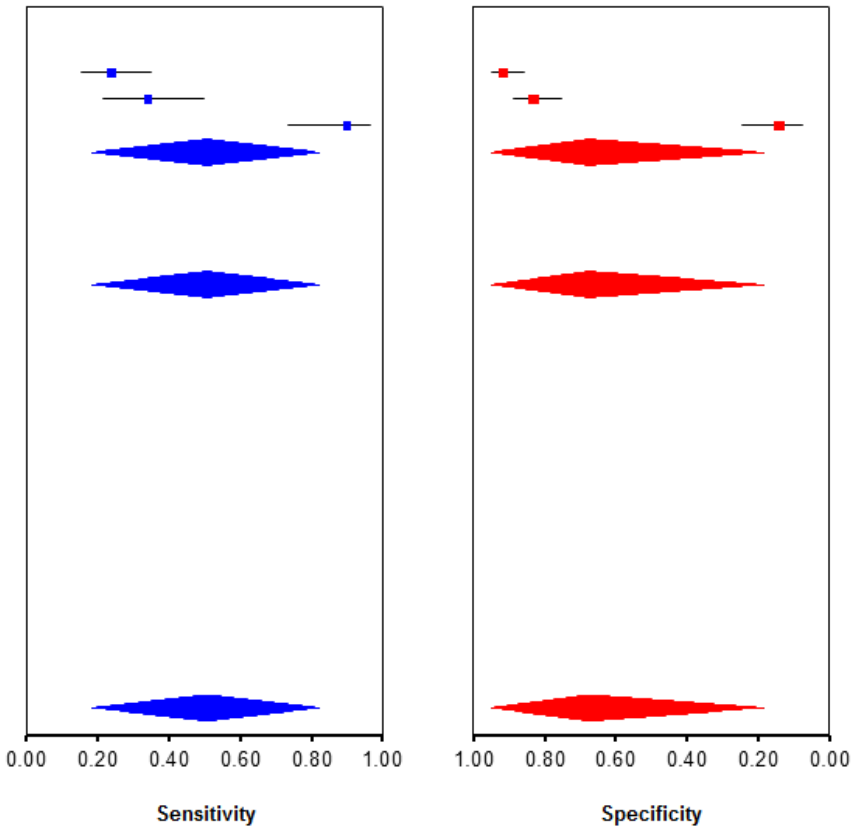


Overall heterogeneity, LR-: Tau²=0.04; Chi²=9.93, df=6 (p=0.128); I²=39.6%
Overall heterogeneity, LR+: Tau²=0.03; Chi²=15.07, df=6 (p=0.020); I²=60.2%

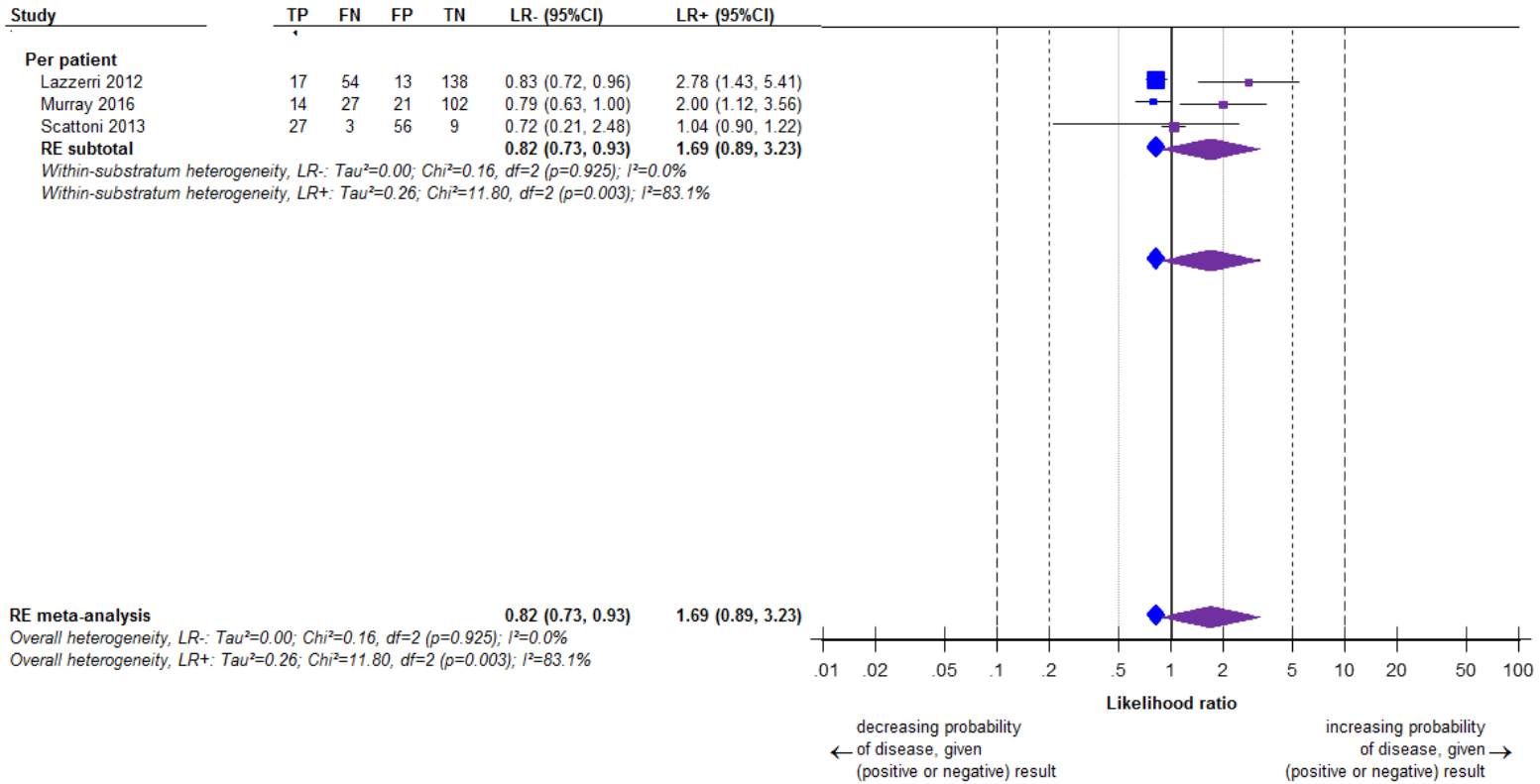
%Free Prostate specific antigen

Threshold 10% sensitivity and specificity

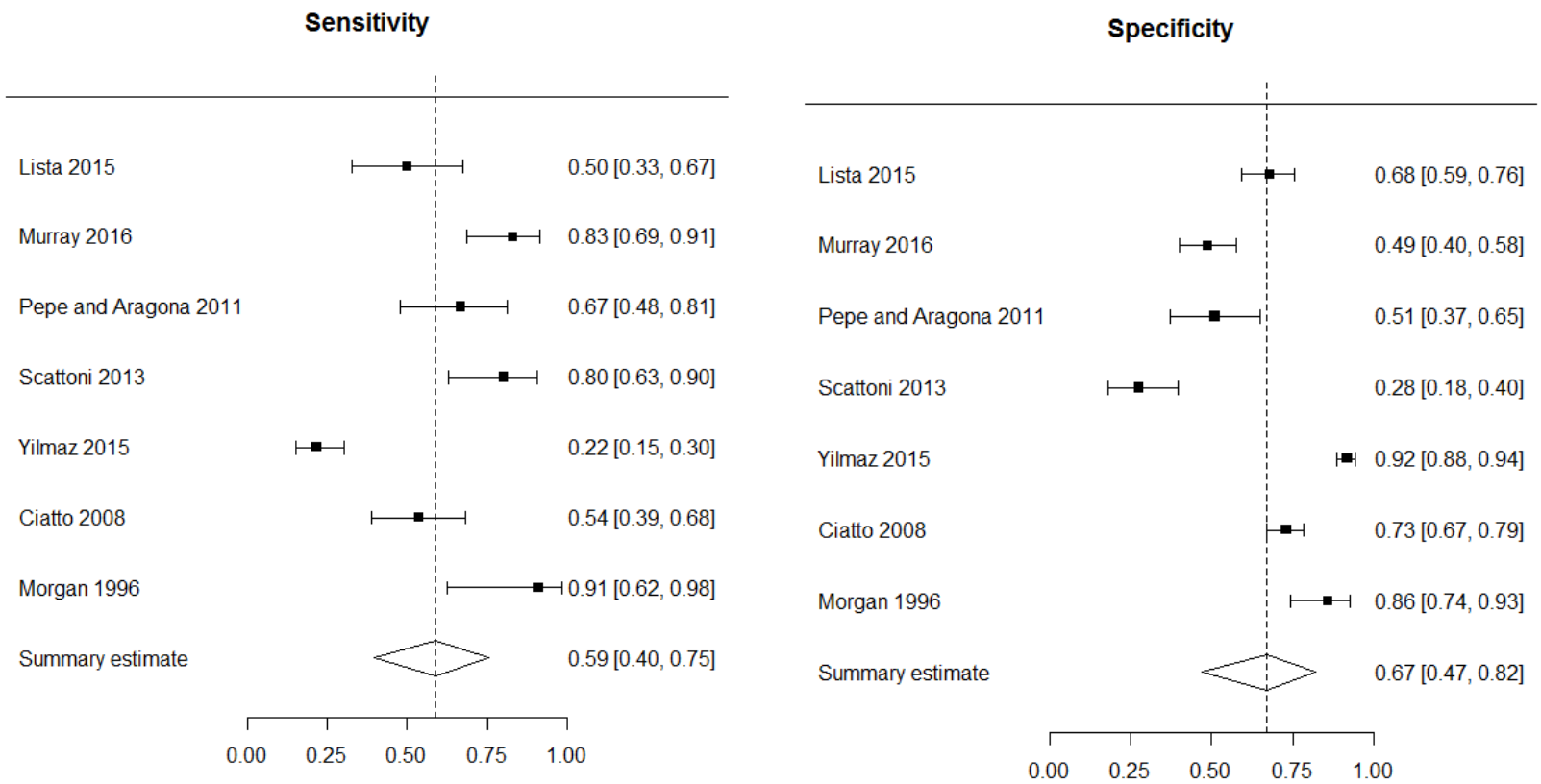
Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Per patient						
Lazzerri 2012	17	54	13	138	0.24 (0.15, 0.35)	0.91 (0.86, 0.95)
Murray 2016	14	27	21	102	0.34 (0.21, 0.50)	0.83 (0.75, 0.89)
Scattoni 2013	27	3	56	9	0.90 (0.73, 0.97)	0.14 (0.07, 0.25)
RE subtotal					**0.51 (0.18, 0.82)**	**0.67 (0.18, 0.95)**
Within-substratum heterogeneity, sens: Tau²=1.61; Chi²=25.15, df=2 (p<0.001); I²=92.0%						
Within-substratum heterogeneity, spec: Tau²=3.73; Chi²=89.42, df=2 (p<0.001); I²=97.8%						
RE meta-analysis					**0.51 (0.18, 0.82)**	**0.67 (0.18, 0.95)**
Overall heterogeneity, sens: Tau²=1.61; Chi²=25.15, df=2 (p<0.001); I²=92.0%						
Overall heterogeneity, spec: Tau²=3.73; Chi²=89.42, df=2 (p<0.001); I²=97.8%						



Threshold <10% positive and negative likelihood ratios

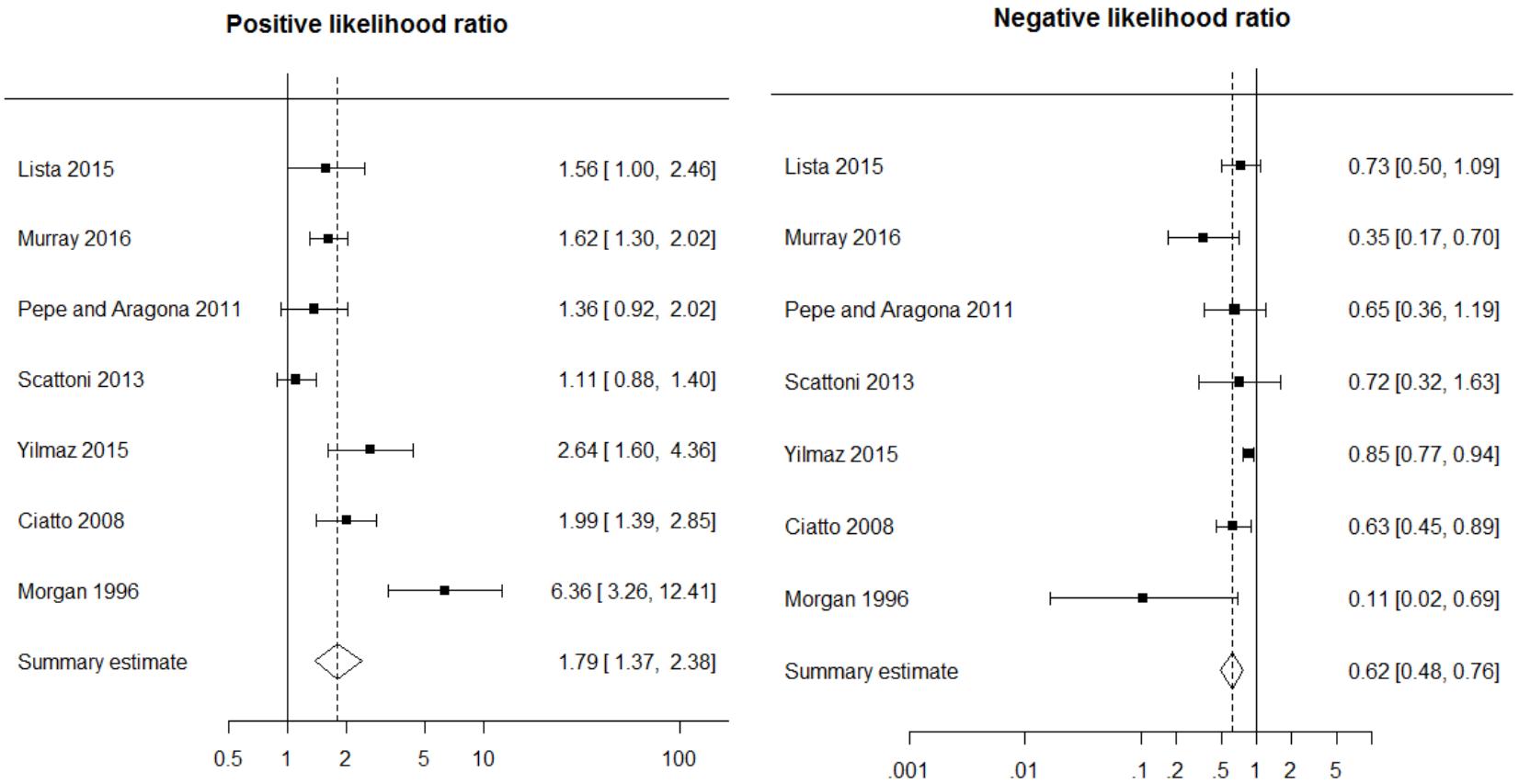


Threshold 15% Sensitivity and specificity



Overall heterogeneity, sens: Tau^2=1.35; Chi^2=63.71, df=6 (p<0.001); I^2=90.6%
Overall heterogeneity, spec: Tau^2=1.06; Chi^2=141.90, df=6 (p<0.001); I^2=95.8%

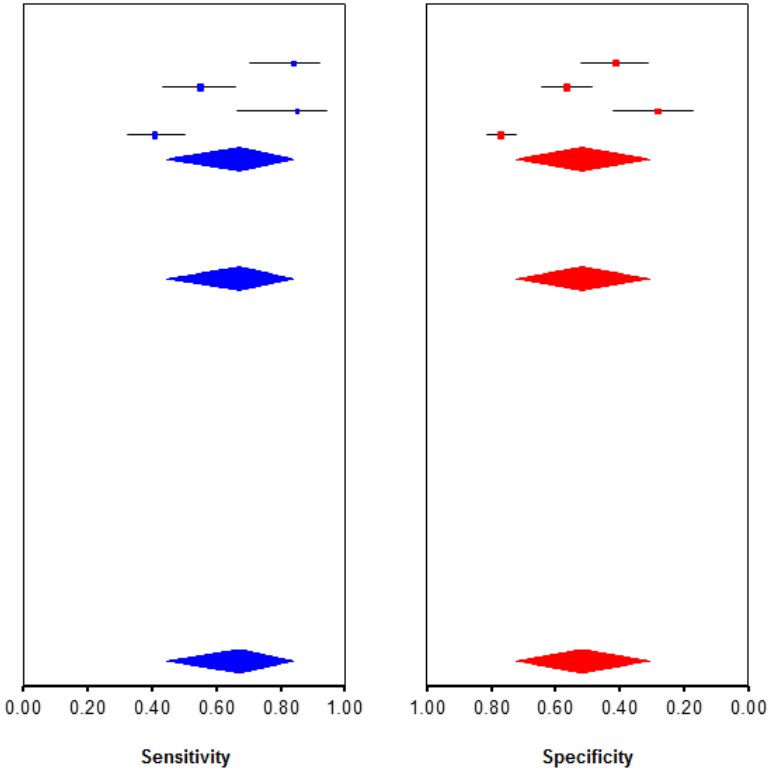
Threshold <15% positive and negative likelihood ratio



Overall heterogeneity, LR-: Tau²=0.05; Chi²=13.84, df=6 (p=0.031); I²=56.7%
Overall heterogeneity, LR+: Tau²=0.13; Chi²=31.86, df=6 (p<0.001); I²=81.2%

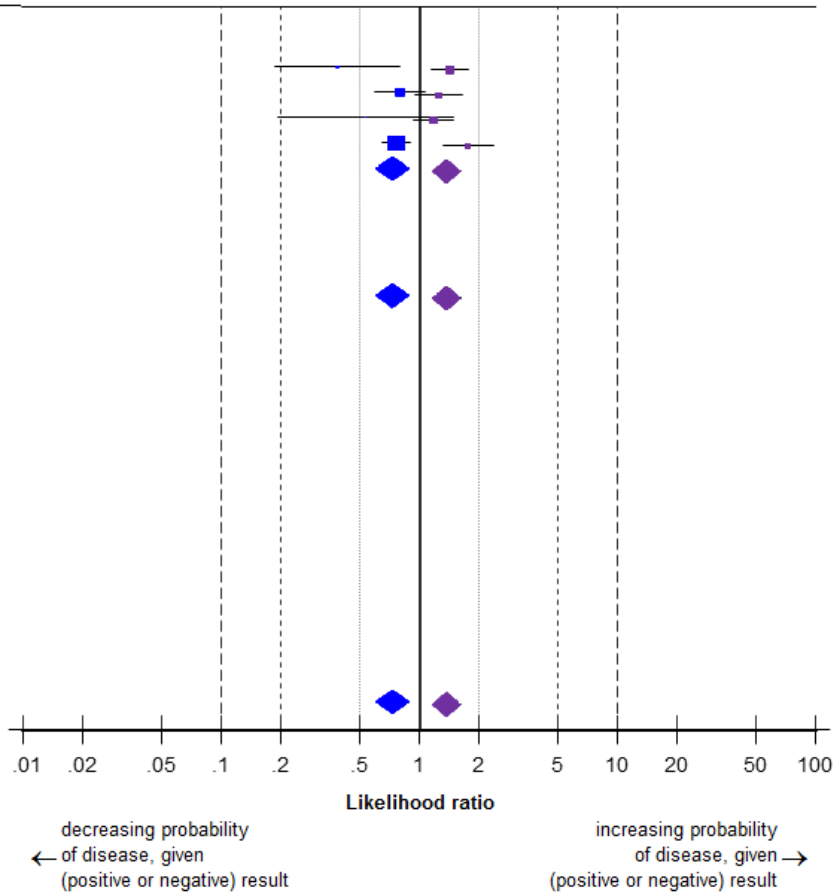
Threshold 20% sensititvity and specificity

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
Auprich 2012	37	7	49	34	0.84 (0.70, 0.92)	0.41 (0.31, 0.52)
Lazzerri 2012	39	32	66	85	0.55 (0.43, 0.66)	0.56 (0.48, 0.64)
Pepe and Aragona 2011	23	4	34	13	0.85 (0.67, 0.94)	0.28 (0.17, 0.42)
Yilmaz 2015	47	68	76	252	0.41 (0.32, 0.50)	0.77 (0.72, 0.81)
RE subtotal					**0.67 (0.45, 0.84)**	**0.52 (0.31, 0.72)**
Within-substratum heterogeneity, sens: Tau^2=0.79; Chi^2=29.75, df=3 (p<0.001); I^2=89.9%						
Within-substratum heterogeneity, spec: Tau^2=0.76; Chi^2=65.89, df=3 (p<0.001); I^2=95.4%						
Per sector						
no data						
RE subtotal					**0.67 (0.45, 0.84)**	**0.52 (0.31, 0.72)**
Within-stratum heterogeneity, sens: Tau^2=0.79; Chi^2=29.75, df=3 (p<0.001); I^2=89.9%						
Within-stratum heterogeneity, spec: Tau^2=0.76; Chi^2=65.89, df=3 (p<0.001); I^2=95.4%						
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
no data						
Per sector						
no data						
RE meta-analysis					**0.67 (0.45, 0.84)**	**0.52 (0.31, 0.72)**
Overall heterogeneity, sens: Tau^2=0.79; Chi^2=29.75, df=3 (p<0.001); I^2=89.9%						
Overall heterogeneity, spec: Tau^2=0.76; Chi^2=65.89, df=3 (p<0.001); I^2=95.4%						

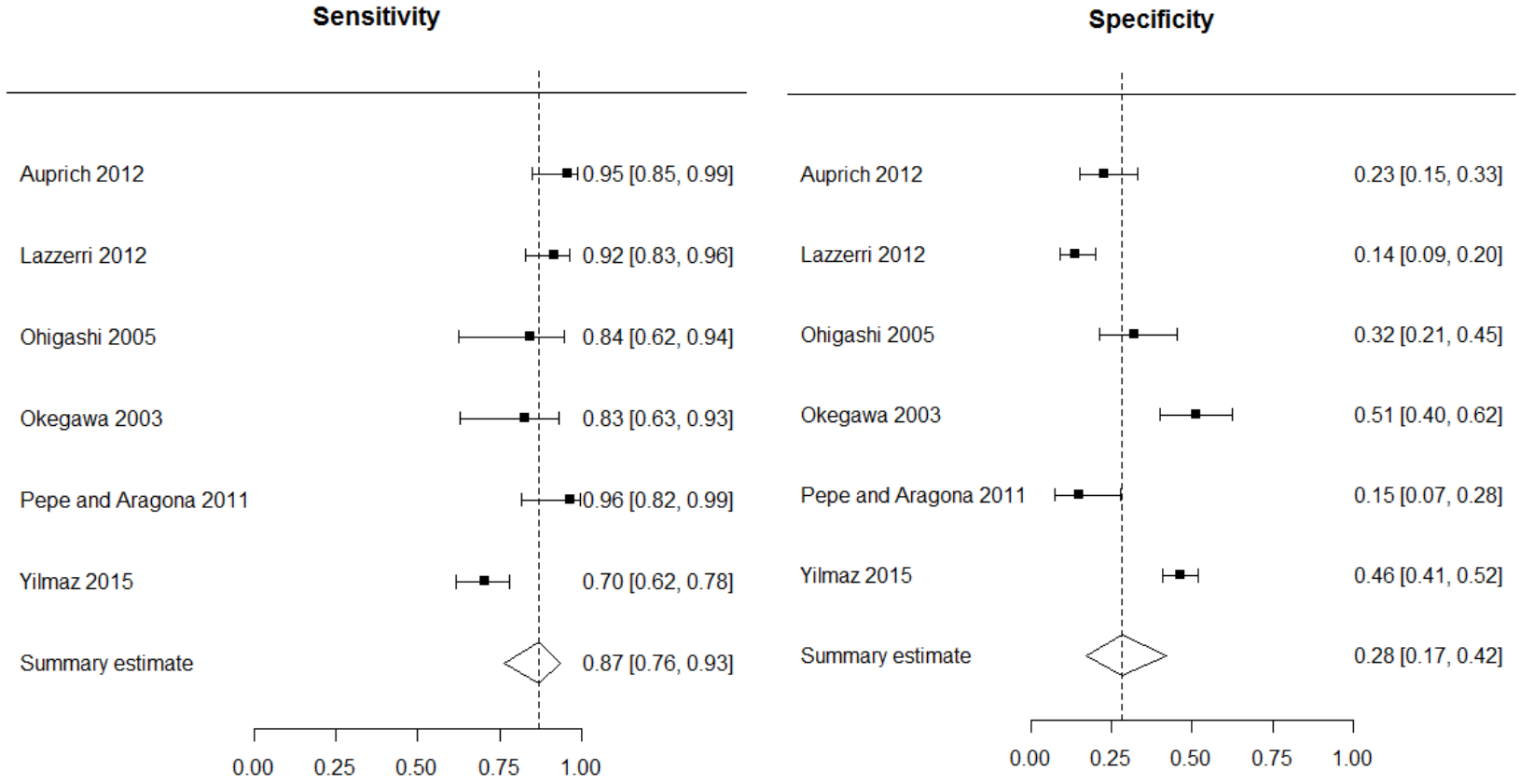


Threshold 20% positive and negative likelihood ratios

Study	TP	FN	FP	TN	LR- (95%CI)	LR+ (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
Auprich 2012	37	7	49	34	0.39 (0.19, 0.80)	1.42 (1.14, 1.78)
Lazzerri 2012	39	32	66	85	0.80 (0.60, 1.07)	1.26 (0.95, 1.66)
Pepe and Aragona 2011	23	4	34	13	0.54 (0.19, 1.48)	1.18 (0.93, 1.49)
Yilmaz 2015	47	68	76	252	0.77 (0.65, 0.91)	1.76 (1.31, 2.37)
RE subtotal					**0.73 (0.60, 0.89)**	**1.37 (1.17, 1.62)**
Within-substratum heterogeneity, LR-: Tau²=0.01; Chi²=3.86, df=3 (p=0.277); I²=22.2%						
Within-substratum heterogeneity, LR+: Tau²=0.01; Chi²=4.88, df=3 (p=0.181); I²=38.5%						
Per sector						
no data						
RE subtotal					**0.73 (0.60, 0.89)**	**1.37 (1.17, 1.62)**
Within-stratum heterogeneity, LR-: Tau²=0.01; Chi²=3.86, df=3 (p=0.277); I²=22.2%						
Within-stratum heterogeneity, LR+: Tau²=0.01; Chi²=4.88, df=3 (p=0.181); I²=38.5%						
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
no data						
Per sector						
no data						
RE meta-analysis					**0.73 (0.60, 0.89)**	**1.37 (1.17, 1.62)**
Overall heterogeneity, LR-: Tau²=0.01; Chi²=3.86, df=3 (p=0.277); I²=22.2%						
Overall heterogeneity, LR+: Tau²=0.01; Chi²=4.88, df=3 (p=0.181); I²=38.5%						

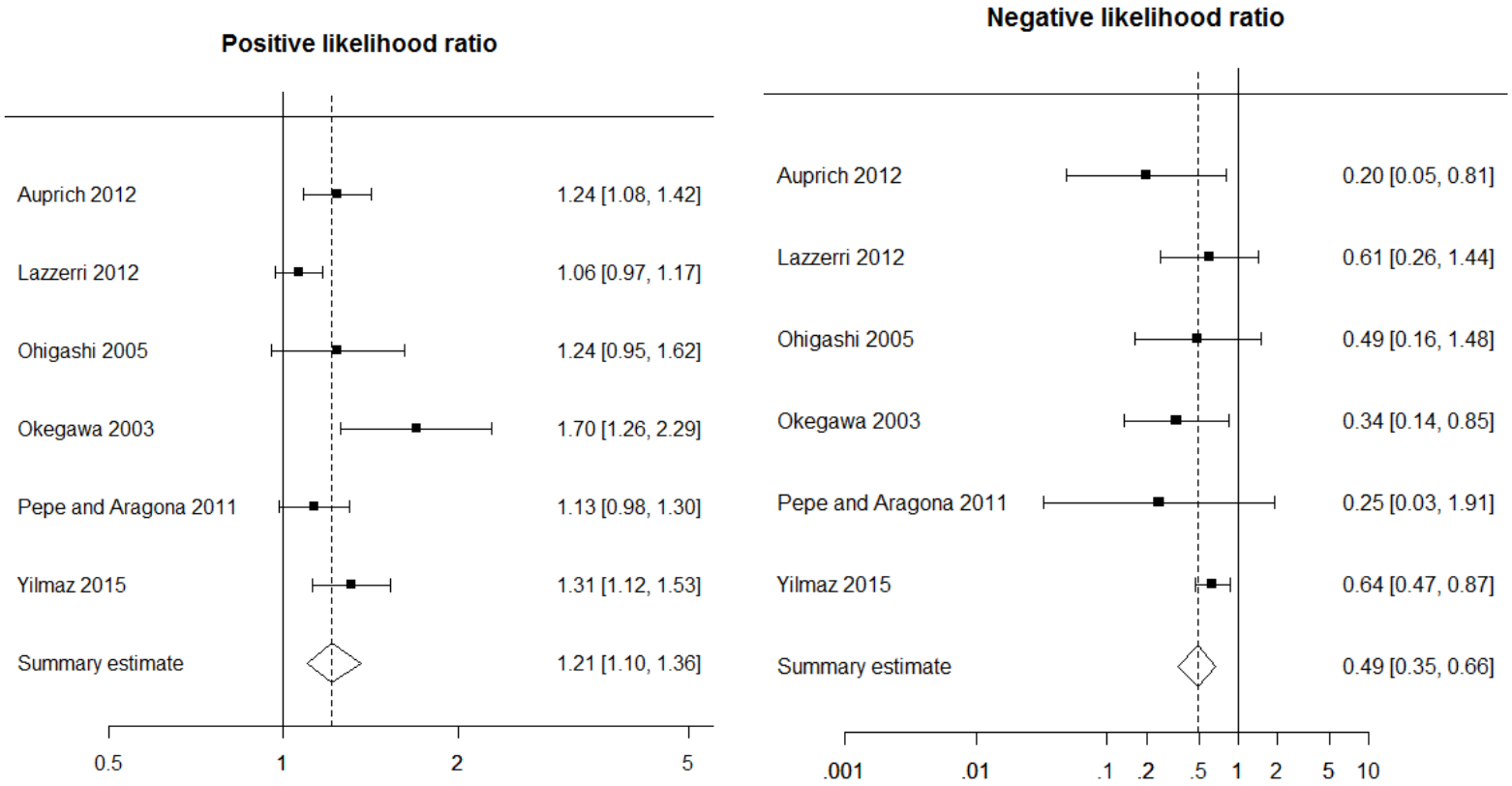


Threshold 25% sensitivity and specificity



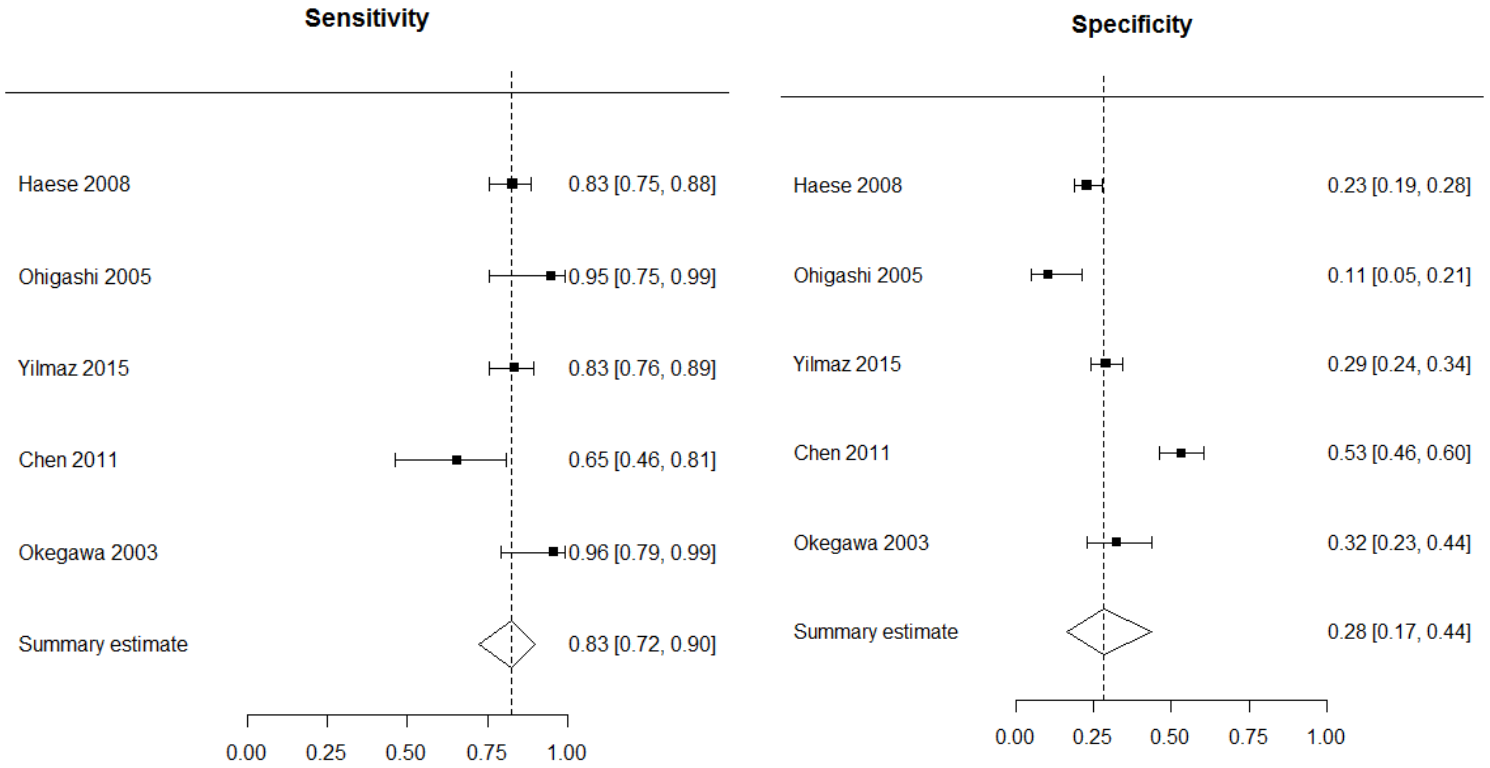
Overall heterogeneity, sens: Tau^2=0.73; Chi^2=20.80, df=5 (p<0.001); I^2=76.0%
Overall heterogeneity, spec: Tau^2=0.60; Chi^2=64.72, df=5 (p<0.001); I^2=92.3%

Threshold 25% positive and negative likelihood ratio



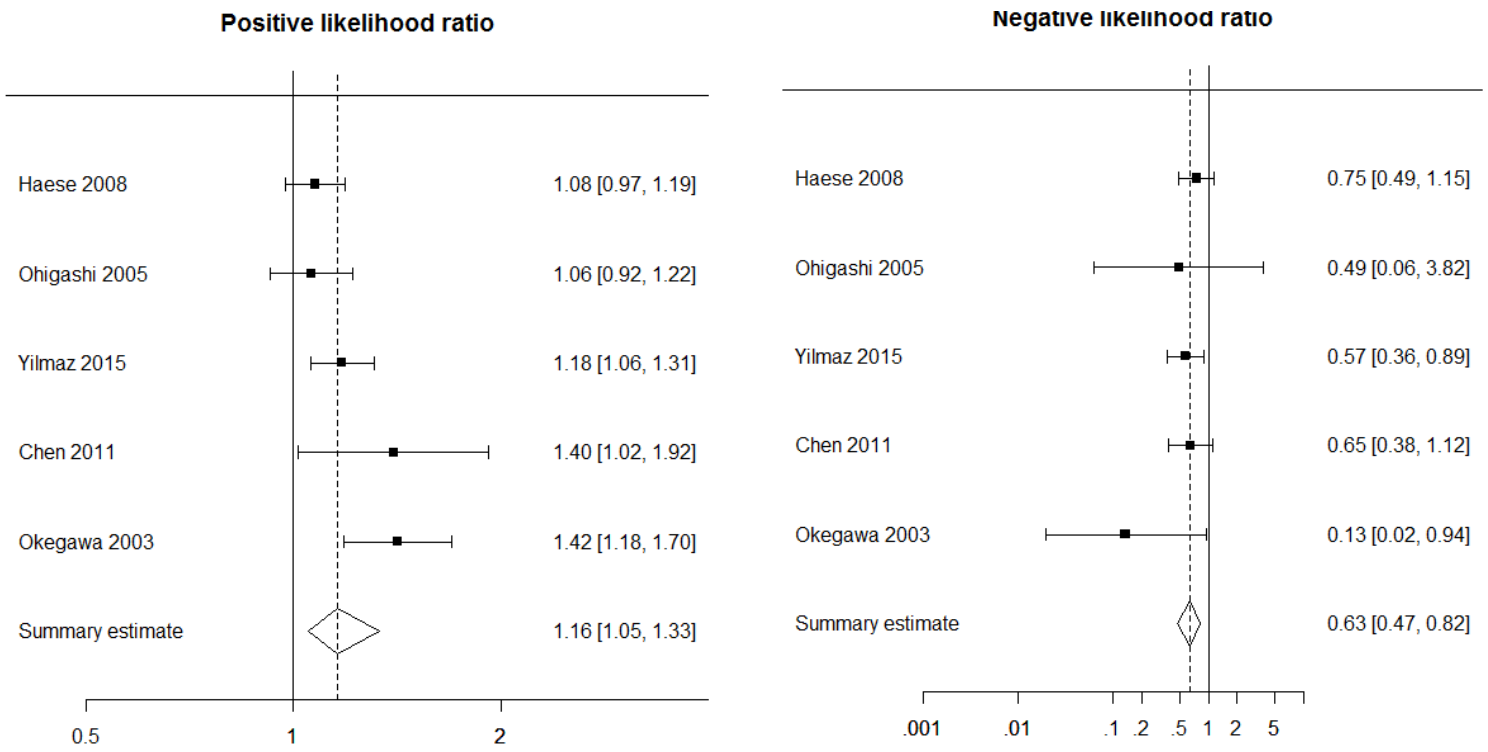
Overall heterogeneity, LR-: Tau²=0.00; Chi²=4.62, df=5 (p=0.463); I²=0.0%
Overall heterogeneity, LR+: Tau²=0.01; Chi²=12.97, df=5 (p=0.024); I²=61.4%

Threshold 30% sensitivity and specificity



Overall heterogeneity, sens: Tau^2=0.18; Chi^2=8.95, df=4 (p=0.062); I^2=55.3%
Overall heterogeneity, spec: Tau^2=0.22; Chi^2=31.33, df=4 (p<0.001); I^2=87.2%

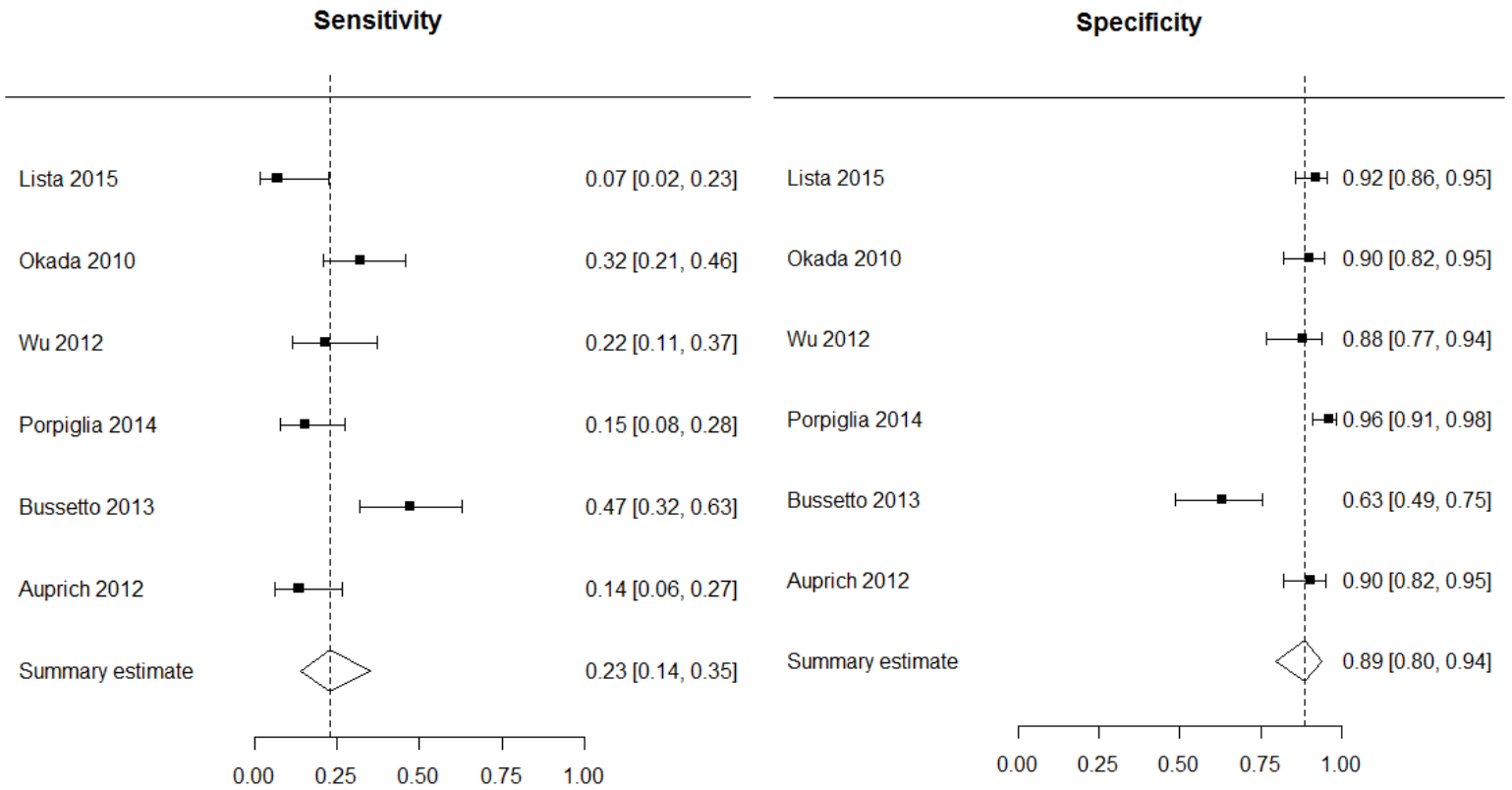
Threshold 30% positive and negative likelihood ratio



Overall heterogeneity, LR-: Tau²=0.05; Chi²=5.94, df=4 (p=0.204); I²=32.6%
Overall heterogeneity, LR+: Tau²=0.04; Chi²=12.72, df=4 (p=0.013); I²=68.5%

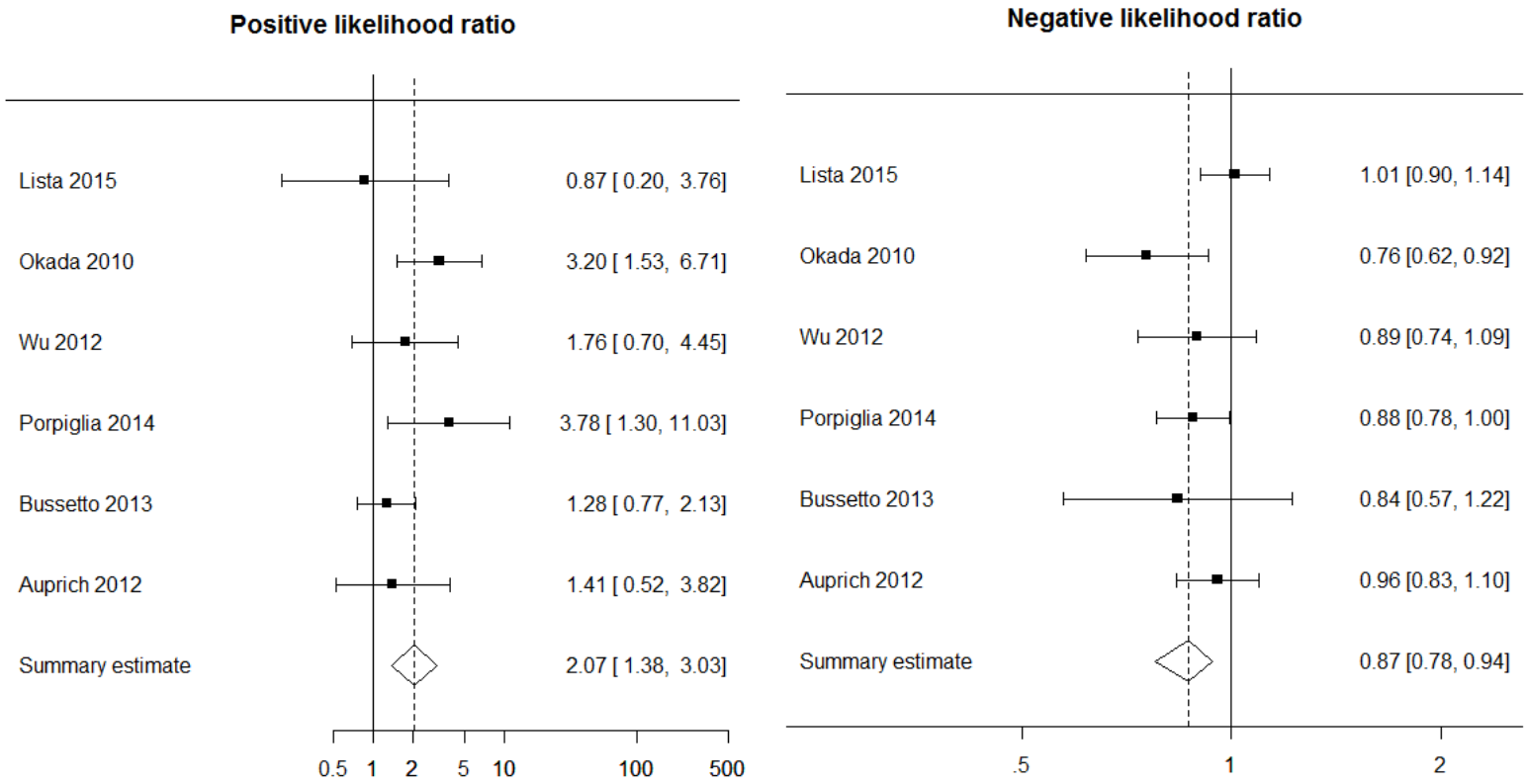
Abnormal digital rectal examination

Positive DRE - Sensitivity and specificity



Overall heterogeneity, sens: Tau^2=0.46; Chi^2=16.14, df=4 (p=0.003); I^2=75.2%
Overall heterogeneity, spec: Tau^2=0.88; Chi^2=30.78, df=4 (p<0.001); I^2=87.0%

Positive DRE- Positive and negative likelihood ratios



Overall heterogeneity, LR-: Tau²=0.01; Chi²=6.93, df=4 (p=0.139); I²=42.3%
Overall heterogeneity, LR+: Tau²=0.13; Chi²=6.85, df=4 (p=0.144); I²=41.6%

Appendix G – GRADE tables

Prostate cancer antigen 3 urinary assay

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate cancer antigen 3 urinary assay cut off 20- (reference standard: biopsy) analysis by person										
10 Studies[4]	Cross sectional studies Retrospective and Prospective	2235	0.89 (0.82, 0.93)	0.30 (0.24, 0.41)	LR+ 1.26 (1.16, 1.39)	Serious[1]	Very Serious[2]	Not serious	Not serious	Very Low
					LR- 0.35 (0.22, 0.38)	Serious[1]	Very Serious[2]	Not serious	Not serious	Very Low
Prostate cancer antigen 3 urinary assay threshold cut off 35 - (reference standard: biopsy) analysis by person										
13 Studies[5])	Retrospective and Prospective Cross sectional studies	3828	0.71 (0.59, 0.81)	0.57 (0.46, 0.66)	LR+ 1.64 (1.36, 1.99)	Serious[1]	Very Serious[2]	Not serious	Not serious	Very Low
					LR- 0.52 (0.37, 0.68)	Serious[1]	Very Serious[2]	Not serious	Serious[3]	Very Low
Prostate cancer antigen 3 urinary assay threshold cut off 50 - (reference standard: biopsy) analysis by person										
10 studies[6]	Cross sectional	1806	0.65(0.53, 0.75)	0.67 (0.57, 0.76)	LR+ 2.01 (1.53, 2.62)	Serious[1]	Very Serious[2]	Not serious	Serious[3]	Very Low
					LR- 0.52 (0.38, 0.68)	Serious[1]	Very Serious[2]	Not serious	Serious[3]	Very Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once 2. The I2 was greater than 66.7%, downgraded twice 3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once 4. 4. Auprich (2012); Barbera (2012); Merola (2015); Marks (2007); Pepe (2012); Pepe and Aragona (2011); Pepe and Aragona (2013); Remzi (2010); Scattoni (2013) 5. Aubin (2010); Auprich (2012); Barrbera (2012), Bollito (2012), Bussetto (2013), Goode (2013), Haese (2008), Kaufmann (2016), Marks (2007),Mereola (2015), Panebianco (2011), Pepe (2012), Pepe and Aragona (2011), Pepe and Aragona (2013), Porpiglia (2014), Remzi (2010), Wu (2012 6. Auprich (2012), Barbera (2012), Bussetto (2013), Haese (2008, Kaufmann (2016), Marks (2007), Mereola (2015), Panebianco (2011), Pepe and Aragona (2011), Wu (2012										

Multiparametric MRI

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Multiparametric MRI score ≥3 - (reference standard: biopsy) analysis by person - any cancer										
4 studies Boesen (2018) Lista (2015) Tsivian (2016) Simmons (2017)	Cross sectional		0.94 (0.91, 0.96)	0.32 (0.24, 0.41)	LR+ 1.36 (1.23, 1.50)	Not Serious	Very serious[2]	Not Serious	Not serious	Low
					LR- 0.18 (0.11, 0.30)	Not Serious	Not Serious	Not serious	Not serious	High
Multiparametric MRI score ≥3 - (reference standard: biopsy) analysis by person - clinically significant cancer										
3 Studies	Cross sectional		0.97 (0.94, 0.99)	0.28 (0.21, 0.36)	LR+ 1.34 (1.20, 1.49)	Not Serious	Very serious[2]	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Boesen (2018) Tsivian (2016) Simmons (2017)					LR- 0.10 (0.04, 0.23)	Not Serious	Not Serious	Not serious	Not serious	High
Multiparametric MRI score ≥4 - (reference standard: biopsy) analysis by person – clinically significant cancer										
2 Studies Boesen (2018) Simmons (2017)	Cross Sectional	538	0.87 (0.71, 0.95)	0.72 (0.65, 0.79)	LR+ 3.11 (2.12, 4.56)	Not Serious	Very serious[2]	Not Serious	Not serious	Low
					LR- 0.18 (0.07, 0.48)	Not Serious	Very serious[2]	Not Serious	Not serious	Low
Multiparametric MRI score 5 - (reference standard: biopsy) analysis by person – clinically significant cancer										
1 study Boesen (2018)	Cross sectional	249	0.57 (0.46, 0.67)	0.97 (0.95, 0.98)	LR+ 16.3 (7.71, 34.5)	Not Serious	N/A	Not Serious	Not serious	High
					LR- 0.45 (0.35, 0.57)	Not Serious	N/A	Not Serious	Not serious	High
Multiparametric MRI score ≥3 - (reference standard: biopsy) analysis per lesion (UCL2)										
1 study Abd Alazeez (2014)	Cross sectional	108 (regions of Interest)	0.76 (0.60, 0.88)	0.42 (0.31, 0.53)	LR+ 1.32 (1.01, 1.72)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 0.56 (0.29, 1.09)	Serious[1]	N/A	Not serious	Not serious	Moderate

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 66.7%, downgraded twice

Total prostate specific antigen

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Total prostate specific antigen (reference standard: biopsy) threshold 4ng/ml										
3 studies Goode (2013) Remzi (2003), Scattoni (2003),	Cross-sectional	1,112	0.90 (0.78, 0.96)	0.10 (0.03, 0.27)	LR+ 1.01 (0.94, 1.09)	Serious[1]	Very serious[2]	Not serious	Serious[4]	Very Low
					LR- 0.90 (0.40, 2.02)	Serious[1]	Very Serious[2]	Not serious	Very Serious[3]	Very Low
Total prostate specific antigen (reference standard: biopsy) threshold 5ng/ml										
3 studies Auprich (2012) Remzi (2003), Okegawa (2003),	Cross-sectional	1,000	0.92 (0.86, 0.96)	0.12 (0.10, 0.14)	LR+ 1.05 (1.00, 1.43)	Serious[1]	Very Serious[2]	Not serious	Not serious	Very Low
					LR- 0.67 (0.37, 1.21)	Serious[1]	Serious[5]	Not serious	Serious[4]	Very Low
Total prostate specific antigen (reference standard: biopsy) threshold 6ng/ml										
4 studies Auprich (2012) Ohigashi (2005) Scattoni (2013) Chen (2011)	Cross-sectional	509	0.83 (0.75, 0.89)	0.30 (0.13, 0.56)	LR+ 1.27 (0.97, 1.67)	Serious[1]	Very serious[2]	Not serious	Not serious	Very Low
					LR- 0.56 (0.31, 1.02)	Serious[1]	Not serious	Not serious	Serious[4]	Low
Total prostate specific antigen (reference standard: biopsy) threshold 7ng/ml										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
3 studies Auprich (2012), Ohigashi (2005), Okegawa (2003)	Cross-sectional	299	0.75 (0.65, 0.83)	0.33 (0.27, 0.40)	LR+ 1.15 (0.96, 1.36)	Serious[1]	Not serious	Not serious	Not serious	Moderate
					LR- 0.78 (0.51, 1.19)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Total prostate specific antigen (reference standard: biopsy) threshold 8.5ng/ml										
1 study Ciatto (2008)	Cross-sectional	355	0.30(0.19, 0.43)	0.72(0.67, 0.77)	LR+1.07 (0.69, 1.66)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR-0.54 (0.18, 1.62)	Serious[1]	N/A	Not serious	Not serious	Moderate

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 66.7%, downgraded twice
3. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
5. The I^2 was greater than 33.3%, downgraded once

Prostate specific antigen Density

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate specific antigen density (reference standard: biopsy) threshold 0.09ng/ml/ml (0.05-0.09ng/ml/ml)										
2 studies Okegawa (2003)	Cross-sectional	1,000	0.95 (0.89, 0.98)	0.15 (0.12, 0.17)	LR+ 1.11 (1.06, 1.17)	Serious[1]	Not serious	Not serious	Not serious	Moderate
					LR- 0.33 (0.14, 0.78)	Serious[1]	Not serious	Not serious	Serious[3]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Remzi (2003)										
Prostate specific antigen density (reference standard: biopsy) threshold ≥0.10ng/ml/ml (0.10-0.14ng/ml/ml)										
3 studies Michielsen (1998) Ohigashi (2005) Remzi (2003)	Cross-sectional	1,066	0.92 (0.86, 0.95)	0.22 (0.19, 0.25)	LR+ 1.17 (1.09, 1.25)	Serious[1]	Not serious	Not serious	Not serious	Moderate
					LR- 0.39 (0.22, 0.68)	Serious[1]	Not serious	Not serious	Serious[3]	Low
Prostate specific antigen density (reference standard: biopsy) threshold ≥0.15ng/ml/ml (0.15-0.20ng/ml/ml)										
7 studies Wu (2012), Boesen (2018), Ohigashi (2005) Keetch (1996) Lista (2015) Okegawa (2003) Chen (2011)	Cross-sectional	1,319	0.73 (0.64, 0.80)	0.52 (0.42, 0.62)	LR+ 1.53 (1.31, 1.81)	Serious[1]	Very Serious[2]	Not serious	Not serious	Very Low
					LR- 0.52 (0.42, 0.65)	Serious[1]	Serious[4]	Not serious	Serious[3]	Very Low
Prostate specific antigen density (reference standard: biopsy) threshold ≥0.30ng/ml/ml (0.30-0.34ng/ml/ml)										
2 studies Okada (2010) Yuasa	Cross-sectional	267	0.66 (0.54, 0.76)	0.76 (0.57, 0.88)	LR+ 2.73 (1.26, 5.88)	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very Low
					LR- 0.46 (0.31, 0.68)	Serious[1]	Not serious	Not serious	Serious[3]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
(2008),										
Prostate specific antigen density (reference standard: biopsy) threshold 0.35ng/ml/ml										
1 study Shaida (2009)	Cross-sectional	67	0.89 (0.66, 0.97)	0.52 (0.38, 0.66)	LR+1.87 (1.34, 2.61)	Serious[1]	N/A	Not serious	Serious[3]	Low
					LR- 0.20 (0.05, 0.77))	Serious[1]	N/A	Not serious	Serious[3]	Low

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 33.3%, downgraded once
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

Prostate specific antigen velocity

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate specific antigen velocity (reference standard: biopsy) threshold ≥0.75ng/ml/year (0.75-0.80ng/ml/year)										
7 studies Auprich (2012) Ciatto (2008) Chen (2011) Keetch (1996) Lista (2015) Shaida (2009)	Cross-sectional	1,364	0.69 (0.57, 0.79)	0.56 (0.43, 0.68)	LR+ 1.57 (1.27,1 97)	Serious[1]	Serious[2]	Not Serious	Not Serious	Low
					LR- 0.57 (0.43, 0.72))	Serious[1]	Serious[2]	Not Serious	Not Serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Yuasa (1998)										
Prostate specific antigen velocity (reference standard: biopsy) threshold 0.28ng/ml/year										
1 study Auprich (2012)	Cross-sectional	127	0.95 (0.84, 0.99)	0.05 (0.02, 0.12)	LR+ 1.00 (0.93, 1.09)	Serious[1]	N/A	Not Serious	Not Serious	Moderate
					LR- 0.94 (0.18, 4.95)	Serious[1]	N/A	Not Serious	Serious[3]	Low
Prostate specific antigen velocity (reference standard: biopsy) threshold 1.19ng/ml/year										
1 study Auprich (2012)	Cross-sectional	127	0.75 (0.60, 0.86)	0.42 (0.32, 0.53)	LR+ 1.30 (1.01, 1.67)	Serious[1]	N/A	Not Serious	Not Serious	Moderate
					LR- 0.59 (0.34, 1.05)	Serious[1]	N/A	Not Serious	Serious[3]	Low

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 33.3%, downgraded once
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

Prostate specific antigen density of the transition zone

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate specific antigen density of the transition zone (reference standard: biopsy) threshold 0.20ng/ml/ml										
2 studies Remzi (2003) Okegawa (2003)	Cross-sectional	1,000	0.95 (0.89, 0.98)	0.21 (0.19, 0.24)	LR+ 1.21 (1.15, 1.28)	Serious[1]	Not serious	Not serious	Not serious	Moderate
					LR- 0.22 (0.09, 0.52)	Serious[1]	Not serious	Not serious	Serious[4]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate specific antigen density of the transition zone (reference standard: biopsy) threshold 25 ng/ml/ml										
2 studies Ohigashi (2005) Remzi (2003)	Cross-sectional	978	0.91 (0.84, 0.95)	0.23 (0.14, 0.35)	LR+ 1.21 (1.13, 1.30)	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
					LR- 0.36 (0.19, 0.67)	Serious[1]	Not serious	Not serious	Not serious	Moderate

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 33.3%, downgraded once
3. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

Prostate health index

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate health index (reference standard: biopsy) threshold 25										
1 Study Scattoni (2003)	Cross-sectional	95	0.90 (0.73, 0.97)	0.08 (0.03, 0.17)	LR+0.98 (0.85, 1.12)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 1.30 (0.33, 5.09)	Serious[1]	N/A	Not serious	Serious	Low
Prostate health index (reference standard: biopsy) threshold 30										
1 Study Lazzeri (2012)	Cross-sectional	222	0.90 (0.81, 0.95)	0.25 (0.19, 0.33)	LR+1.20 (1.07, 1.36)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 0.39 (0.18, 0.83)	Serious[1]	N/A	Not serious	Serious	Low
Prostate health index (reference standard: biopsy) threshold 35										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Study Scattoni (2003)	Cross-sectional	95	0.80 (0.62, 0.91)	0.48 (0.36, 0.60)	LR+1.53 (1.14, 2.05)	Serious[1]	N/A	Not serious	Serious[2]	Low
					LR- 0.42 (0.20, 0.90)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate health index (reference standard: biopsy) threshold 40										
1 Study Lazzeri (2012)	Cross-sectional	222	0.62 (0.50, 0.72)	0.60 (0.52, 0.67)	LR+1.53 (1.18, 2.00)	Serious[1]	N/A	Not serious	Very Serious[4]	Very Low
					LR- 0.64 (0.46, 0.88)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate health index (reference standard: biopsy) threshold 48.9										
1 study Porpiglia (2014)	Cross-sectional	170	0.40 (0.28, 0.54)	0.78 (0.70, 0.85)	LR+ 1.83 (1.14, 2.94)	Serious[1]	N/A	Not serious	Serious	Moderate
					LR- 0.76 (0.60, 0.98)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate health index (reference standard: biopsy) threshold 62										
1 study Lazzeri (2012)	Cross-sectional	222	0.30 (0.20, 0.41)	0.91 (0.85, 0.94)	LR+ 3.19 (1.73, 5.90)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR-0.78 (0.66, 0.91)	Serious[1]	N/A	Not serious	Not serious	Moderate

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

Prostate Health Index in MRI negative and biopsy naive population

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate health index (reference standard: biopsy) threshold 25										
1 Study Gnanapragasm (2016)	Cross-sectional	94	0.97 (0.79, 1.00)	0.11(0.05, 0.21)	LR+ 1.08 (0.97, 1.21)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR-0.32 (0.04, 2.48)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate health index (reference standard: biopsy) threshold 30										
1 Study Gnanapragasm (2016)	Cross-sectional	94	0.95 (0.82, 0.99)	0.26(0.16, 0.40)	LR+ 1.29 (1.08, 1.54)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 0.18 (0.04, 0.77)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate health index (reference standard: biopsy) threshold 35										
1 Study Gnanapragasm (2016)	Cross-sectional	94	0.94 (0.84, 0.98)	0.43 (0.29, 0.58)	LR+ 1.65 (1.26, 2.16)	Serious[1]	N/A	Not serious	Serious[2]	Moderate
					LR- 0.13 (0.04, 0.43)	Serious[1]	N/A	Not serious	Not serious	Very Low
Prostate health index (reference standard: biopsy) threshold 40										
1 Study Gnanapragasm (2016)	Cross-sectional	94	0.76 (0.65, 0.85)	0.65 (0.46,0.81)	LR+ 2.21 (1.28, 3.81)	Serious[1]	N/A	Not serious	Very Serious[3]	Very Low
					LR- 0.36 (0.22, 0.60)	Serious[1]	N/A	Not serious	Serious[2]	Low

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
3. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice

Percent free prostate specific antigen

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
% free Prostate specific antigen (reference standard: Biopsy) threshold 10% (5-9%)										
3 Studies Lazzeri (2012) Murray (2016), Scattoni (2003),	Cross-sectional	481	0.51 (0.18, 0.82)	0.67 (0.18, 0.95)	LR+ 1.69 (0.89, 3.23)	Serious[1]	Very Serious[2]	Not serious	Very serious	Very Low
					LR- 0.82 (0.73, 0.93)	Serious[1]	Not serious	Not serious	Serious[3]	Very Low
% free Prostate specific antigen (reference standard: Biopsy) threshold 15% (10-14%)										
7 studies Ciatto (2008) Lista (2015) Morgan (1996) Murray (2016) Pepe and Aragona (2011) Scattoni (2013) Yilmaz (2015)	Cross-sectional	1,253	0.59 (0.40, 0.75)	0.67 (0.47, 0.82)	LR+1.79 (1.37, 2.38)	Serious[1]	Very serious[2]	Not serious	Serious[4]	Very Low
					LR-0.62 (0.48, 0.76)	Serious[1]	Serious[5]	Not serious	Not serious	Low
% free Prostate specific antigen (reference standard: Biopsy) threshold 20% (15-19%)										
4 studies	Cross-sectional	720	0.67 (0.45, 0.84)	0.52 (0.31, 0.72)	LR+1.37 (1.17, 1.62)	Serious[1]	Very serious[2]	Not serious	Not serious	Very Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Auprich (2012), Yilmaz (2015), Lazzeri (2012) Pepe and Aragona (2011)					LR-0.73 (0.60, 0.89)	Serious[1]	Very serious[2]	Not Serious	Serious[4]	Very Low
% free Prostate specific antigen (reference standard: Biopsy) threshold 25% (20-24%)										
6 studies Auprich (2012) Lazzeri (2012) Ohigashi (2005) Pepe and Aragona (2011) Yilmaz (2015)	Cross Sectional	1,038	0.86 (0.76, 0.93)	0.28 (0.17, 0.42)	LR+1.21 (1.10, 1.36)	Serious[1]	Not serious	Not serious	Not serious	Moderate
					LR-0.49 (0.35, 0.66)	Serious[1]	Not serious	Not serious	Not serious	Moderate
% free Prostate specific antigen (reference standard: Biopsy) threshold 30% (25-29%)										
5 Studies Yilmaz (2015) Chen (2011) Haese (2008)	Cross Sectional	1,290	0.83 (0.72, 0.90)	0.28 (0.17, 0.44)	LR+1.16 (1.05, 1.33)	Serious[1]	Very Serious[3]	Not serious	Not serious	Very Low
					LR-0.63 (0.47, 0.82)	Serious[1]	Not serious	Not serious	Serious[4]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Okegawa (2003) Ohigashi (2005)										
% free Prostate specific antigen (reference standard: Biopsy) threshold 35% (30-34%)										
1 Study Remzi 2003	Cross sectional	820	0.95(0.88, 0.98)	0.34 (0.30, 0.37)	LR+1.43 (1.34, 1.53)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR-0.14 (0.05, 0.38)	Serious[1]	N/A	Not serious	Not serious	Moderate
% free Prostate specific antigen (reference standard: Biopsy) threshold 38%										
1 Study Remzi 2003	Cross sectional	820	0.90 (0.82, 0.95)	0.50 (0.47, 0.53)	LR+1.81 (1.64, 1.99)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR-0.19 (0.10,0.37)	Serious[1]	N/A	Not serious	Not serious	Moderate

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 66.7%, downgraded twice
3. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
5. The I^2 was greater than 33.3%, downgraded once

PSA doubling time

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate specific antigen doubling time (reference standard: biopsy) 24 months										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study Ciatto (2008)	Cross sectional	355	0.47 (0.35, 0.60)	0.36 (0.31, 0.42)	LR+ 0.74 (0.56, 0.98)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 1.47 (1.01, 1.96)	Serious[1]	N/A	Not serious	Not serious	Moderate
Prostate specific antigen doubling time (reference standard: biopsy) 30 months										
1 study Shimbo (2009)	Cross sectional	77	0.37(0.21, 0.56)	0.40 (0.14, 0.41)	LR+ 0.62 (0.36, 1.06)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 1.54 (1.01, 2.46)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate specific antigen doubling time (reference standard: biopsy) 50 months										
1 study Shimbo (2009)	Cross sectional	77	0.30 (0.16, 0.49)	0.42 (0.29, 0.56)	LR+ 0.51 (0.27, 0.96)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 1.68 (1.12, 2.52)	Serious[1]	N/A	Not serious	Serious[2]	Low
Prostate specific antigen doubling time (reference standard: biopsy) 70 months										
1 study Shimbo (2009)	Cross sectional	77	0.11 (0.04, 0.29)	0.42 (0.29, 0.56)	LR+ 0.19 (0.06, 0.57)	Serious[1]	N/A	Not serious	Not serious	Moderate
					LR- 2.12 (1.49, 3.01)	Serious[1]	N/A	Not serious	Serious[2]	Low

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

Digital Rectal Examination

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Digital rectal examination (reference standard: biopsy) Positive DRE (abnormal)										
6 studies Okada (2009), Wu (2012) Bussetto (2013) Porpiglia 2014 Lista (2015)	Cross-sectional		0.23 (0.14. 0.35)	0.89 (0.80, 0.94)	LR+2.07 (1.38, 3.03)	Serious[1]	Serious[2]	Not serious	Serious[3]	Very Low
					LR- 0.87 (0.78, 0.93)	Serious[1]	Serious[2]	Not serious	Serious[3]	Very Low

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I^2 was greater than 33.3%, downgraded once
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

Appendix H – Excluded studies

Clinical studies

Short Title	Title	Reason for exclusion
Abdalla (1998)	Comparison of serum prostate-specific antigen levels and PSA density in African-American, white, and hispanic men without prostate cancer	Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Abdel-Khalek (2004)	Is extended 11-core biopsy valuable in benign prostatic hyperplasia patients with intermediate serum prostate-specific antigen (4.1-10 ng/ml) and prior negative sextant biopsy?	Participants were biopsy /MRI naive candidates
Abdi (2015)	Multiparametric magnetic resonance imaging-targeted biopsy for the detection of prostate cancer in patients with prior negative biopsy results	Study does not contain any relevant index tests Study looked mp-MRI - targeted TRUS-B
Adam (2011)	The role of the PCA3 assay in predicting prostate biopsy outcome in a South African setting	Participants were biopsy /MRI naive candidates
Ahyai (2010)	The presence of prostate cancer on saturation biopsy can be accurately predicted	Not possible to calculate a 2x2 table from data presented in the study
Al (2008)	Role of repeated biopsy of the prostate in predicting disease progression in patients with prostate cancer on active surveillance	Not possible to calculate a 2x2 table from data presented in the study
Al-Ghazo (2005)	Ultrasound-guided transrectal extended prostate biopsy: a prospective study	Study does not contain any relevant index tests
Allhoff (1993)	Efficient pathway for early detection of prostate cancer concluded from a 5-year prospective study	Participants were biopsy /MRI naive candidates
Amirrasouli (2010)	Accurate cut-off point for free to total prostate-specific antigen ratio used to improve differentiation of prostate cancer from benign prostate hyperplasia in Iranian population	Participants were biopsy /MRI naive candidates
Amsellem-Ouazana (2005)	Negative prostatic biopsies in patients with a high risk of prostate cancer. Is the combination of endorectal MRI and magnetic resonance spectroscopy imaging (MRSI) a useful tool? A preliminary study	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2

Short Title	Title	Reason for exclusion
Anastasiadis (2006)	MRI-Guided Biopsy of the Prostate Increases Diagnostic Performance in Men with Elevated or Increasing PSA Levels after Previous Negative TRUS Biopsies	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Andriole (2011)	The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: results from the REDUCE study	Study does not contain any relevant index tests
Ankerst (2016)	Serial Percent Free Prostate Specific Antigen in Combination with Prostate Specific Antigen for Population Based Early Detection of Prostate Cancer	Participants were biopsy /MRI naive candidates
Arai (1997)	Prospective evaluation of prostate specific antigen density and systematic biopsy for detecting prostate cancer in Japanese patients with normal rectal examinations and intermediate prostate specific antigen levels	Participants were biopsy /MRI naive candidates
Arsov (2012)	Repeat transrectal ultrasound biopsies with additional targeted cores according to results of functional prostate MRI detects high-risk prostate cancer in patients with previous negative biopsy and increased PSA - a pilot study	only patients with suspicious lesions went through with the biopsy
Arumainayagam (2013)	Multiparametric MR imaging for detection of clinically significant prostate cancer: A validation cohort study with transperineal template prostate mapping as the reference standard	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Aubin (2011)	Prostate cancer gene 3 score predicts prostate biopsy outcome in men receiving dutasteride for prevention of prostate cancer: Results from the REDUCE trial	Study not investigating prostate cancer
Ayyildiz (2017)	Serum proPSA as a marker for reducing repeated prostate biopsy numbers	Participants were biopsy /MRI naive candidates
Aziz (1993)	Prostate-specific antigen and prostate volume: a meta-analysis of prostate cancer screening criteria	Participants were biopsy /MRI naive candidates
Bakardzhiev (2012)	Repeat transrectal prostate biopsies in diagnosing prostate cancer	Not possible to calculate a 2x2 table from data

Short Title	Title	Reason for exclusion
		presented in the study
Baltaci (2003)	Use of percent free prostate-specific antigen density to improve the specificity for detecting prostate cancer in patients with normal rectal examinations and intermediate prostate-specific antigen levels	Participants were biopsy /MRI naive candidates
Basillote (2003)	Influence of prostate volume in the detection of prostate cancer	Not possible to calculate a 2x2 table from data presented in the study
Benecchi (2008)	A Novel Nomogram to Predict the Probability of Prostate Cancer on Repeat Biopsy	Not possible to calculate a 2x2 table from data presented in the study
Benecchi (2008)	Optimal measure of PSA kinetics to identify prostate cancer	Study does not contain any relevant index tests
Benecchi (2011)	Evaluation of prostate specific antigen acceleration for prostate cancer diagnosis	Biopsy naive participants
Beyersdorff (2002)	Patients with a history of elevated prostate-specific antigen levels and negative transrectal US-guided quadrant or sextant biopsy results: value of MR imaging	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Bhindi (2017)	Creation and internal validation of a biopsy avoidance prediction tool to aid in the choice of diagnostic approach in patients with prostate cancer suspicion	Study does not contain any relevant index tests
Boegemann (2016)	The percentage of prostate-specific antigen (PSA) isoform [-2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged <=65 years	Not possible to calculate a 2x2 table from data presented in the study
Boesen (2017)	A Prospective Comparison of Selective Multiparametric Magnetic Resonance Imaging Fusion-Targeted and Systematic Transrectal Ultrasound-Guided Biopsies for Detecting Prostate Cancer in Men Undergoing Repeated Biopsies	MRI as the index test only suspicious lesions went through to biopsy
Bokhorst (2012)	Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial*	Not possible to calculate a 2x2 table from data presented in the study

Short Title	Title	Reason for exclusion
Borboroglu (2000)	Extensive repeat transrectal ultrasound guided prostate biopsy in patients with previous benign sextant biopsies	Study does not contain any relevant index tests
Borkowetz (2015)	Assessment of tumour aggressiveness in tranperineal mri/ultrasound-fusion biopsy in comparison to transrectal systematic prostate biopsy	Conference abstract
Boulos (2001)	Should prostate-specific antigen or prostate-specific antigen density be used as the determining factor when deciding which prostates should undergo biopsy during prostate ultrasound	Participants were biopsy /MRI naive candidates
Brown (2014)	Reflex PCA3 messenger ribonucleic acid testing: validation of postbiopsy urine samples and correlation with prostate biopsy findings in ~2000 patients	Participants were biopsy /MRI naive candidates
Busby (2004)	Determining variables for repeat prostate biopsy	Review article but not a systematic review
Campos-Fernandes (2009)	Prostate Cancer Detection Rate in Patients with Repeated Extended 21-Sample Needle Biopsy	Not possible to calculate a 2x2 table from data presented in the study
Carver (2004)	Race is not a predictor of prostate cancer detection on repeat prostate biopsy	Study does not contain any relevant index tests
Catalona (1997)	Serum free prostate specific antigen and prostate specific antigen density measurements for predicting cancer in men with prior negative prostatic biopsies	Not possible to calculate a 2x2 table from data presented in the study only sensitivity figures and cutoffs provided
Celhay (2007)	Fluctuating prostate-specific antigen levels in patients with initial negative biopsy: should we be reassured?	Not possible to calculate a 2x2 table from data presented in the study
Chang (2017)	The Influence of Serum Prostate-Specific Antigen on the Accuracy of Magnetic Resonance Imaging Targeted Biopsy versus Saturation Biopsy in Patients with Previous Negative Biopsy	Not a relevant study design (diagnostic test accuracy) Case control design
Cheikh (2009)	Evaluation of T2-weighted and dynamic contrast-enhanced MRI in localizing prostate cancer before repeat biopsy	Biopsy naive participants
Chen (2015)	Age-Specific Cutoff Value for the Application of Percent Free Prostate-Specific Antigen (PSA) in Chinese	Biopsy naive participants

Short Title	Title	Reason for exclusion
	Men with Serum PSA Levels of 4.0-10.0 ng/ml	
Ciatto (2001)	Predicting prostate biopsy outcome by findings at digital rectal examination, transrectal ultrasonography, PSA, PSA density and free-to-total PSA ratio in a population-based screening setting	Participants were biopsy /MRI naive candidates
Ciatto (2004)	Predictors of random sextant biopsy outcome in screened men with PSA > 4 ng/mL and a negative sextant biopsy at previous screening. Experience in a population-based screening program in Florence	Not possible to calculate a 2x2 table from data presented in the study Participants were biopsy /MRI naive candidates
Ciatto (2004)	Free to total PSA ratio is not a reliable predictor of prostate biopsy outcome	Not possible to calculate a 2x2 table from data presented in the study
Cirillo (2008)	Value of endorectal MRI and MRS in patients with elevated prostate-specific antigen levels and previous negative biopsies to localize peripheral zone tumours	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Collins (1999)	Free prostate-specific antigen 'in the field': a useful adjunct to standard clinical practice	Biopsy naive participants
Comet-Batlle (2003)	The value of endorectal MRI in the early diagnosis of prostate cancer	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Cookson (1995)	The lack of predictive value of prostate specific antigen density in the detection of prostate cancer in patients with normal rectal examinations and intermediate prostate specific antigen levels	Participants were biopsy /MRI naive candidates
Costa (2013)	Diagnosis of relevant prostate cancer using supplementary cores from magnetic resonance imaging-prompted areas following multiple failed biopsies	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Costa (2017)	An initial negative round of targeted biopsies in men with highly suspicious multiparametric magnetic resonance findings does not exclude clinically significant prostate cancer-Preliminary experience	Participants were biopsy /MRI naive candidates
Crawford (2012)	Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: A prospective study of 1,962 cases	Participants were biopsy /MRI naive candidates

Short Title	Title	Reason for exclusion
Dason (2016)	Transurethral Resection of the Prostate Biopsy of Suspected Anterior Prostate Cancers Identified by Multiparametric Magnetic Resonance Imaging: A Pilot Study of a Novel Technique	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
De La Taille (2011)	Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions	Participants were biopsy /MRI naive candidates
De Luca (2012)	Histological chronic prostatitis and high-grade prostate intra-epithelial neoplasia do not influence urinary prostate cancer gene 3 score	Study not investigating prostate cancer Histological chronic prostatitis and high-grade prostate intra-epithelial neoplasia
De Luca (2014)	Comparison of prostate cancer gene 3 score, prostate health index and percentage free prostate-specific antigen for differentiating histological inflammation from prostate cancer and other non-neoplastic alterations of the prostate at initial Biopsy	Participants were biopsy /MRI naive candidates
De Luca (2015)	Prostate health index and prostate cancer gene 3 score but not percent-free Prostate Specific Antigen have a predictive role in differentiating histological prostatitis from PCa and other nonneoplastic lesions (BPH and HG-PIN) at repeat biopsy	Not investigating prostate cancer
De Luca (2015)	Pathological patterns of prostate biopsy in men with fluctuations of prostate cancer gene 3 score: a preliminary report	Not possible to calculate a 2x2 table from data presented in the study
De Visschere (2016)	What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging?	Not possible to calculate a 2x2 table from data presented in the study
Deliktas (2017)	What should be the prostate specific antigen threshold for prostate biopsy?	Participants were biopsy /MRI naive candidates
Deliveliotis (2002)	Biopsies of the transitional zone of the prostate: Should it be done on a routine basis, when and why?	Participants were biopsy /MRI naive candidates
Deras (2008)	PCA3: a molecular urine assay for predicting prostate biopsy outcome	Participants were biopsy /MRI naive candidates
Dincel (1999)	Prospective evaluation of prostate specific antigen (PSA), PSA density, free-to-total PSA ratio and a new formula (prostate malignancy index)	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with

Short Title	Title	Reason for exclusion
	for detecting prostate cancer and preventing negative biopsies in patients with normal rectal examinations and intermediate PSA levels	no stratification
Djavan (1998)	Prostate specific antigen density of the transition zone for early detection of prostate cancer	Biopsy naive participants
Djavan (1999)	Combination and multivariate analysis of PSA-based parameters for prostate cancer prediction	Participants prostate cancer/prostate biopsy history unclear/unknown
Djavan (1999)	PSA, PSA density, PSA density of transition zone, free/total PSA ratio, and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL	Participants were biopsy /MRI naive candidates
Djavan (1999)	Total and transition zone prostate volume and age: how do they affect the utility of PSA-based diagnostic parameters for early prostate cancer detection?	Participants were biopsy /MRI naive candidates
Djavan (2000)	Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men	Participants were biopsy /MRI naive candidates
Djavan (2001)	Pathological features of prostate cancer detected on initial and repeat prostate biopsy: results of the prospective European Prostate Cancer Detection study	Study does not contain any relevant index tests
Djavan (2002)	Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial	Participants were biopsy /MRI naive candidates
Djavan (2005)	Are repeat biopsies required in men with PSA levels < or =4 ng/ml? A Multiinstitutional Prospective European Study	Participants were biopsy /MRI naive candidates
Druskin (2017)	Prostate mri prior to radical prostatectomy: Effects on nerve sparing and pathological margin status	Not a relevant study design (diagnostic test accuracy)
Durand (2011)	What information can a PCA3 urine test provide in the diagnosis and treatment of prostate cancer?	Review article but not a systematic review
Durkan (1999)	Elevated serum prostate specific antigen levels in conjunction with an	Not possible to calculate a 2x2 table from data

Short Title	Title	Reason for exclusion
	initial prostatic biopsy negative for carcinoma: who should undergo a repeat biopsy?	presented in the study
Durmus (2013)	MRI-guided biopsy of the prostate: Correlation between the cancer detection rate and the number of previous negative TRUS biopsies	Not possible to calculate a 2x2 table from data presented in the study
Dwivedi (2012)	A positive magnetic resonance spectroscopic imaging with negative initial biopsy may predict future detection of prostate cancer	Not possible to calculate a 2x2 table from data presented in the study Not a relevant study design (diagnostic test accuracy)
Eggener (2005)	Predictors of subsequent prostate cancer in men with a prostate specific antigen of 2.6 to 4.0 ng/ml and an initially negative biopsy	Not possible to calculate a 2x2 table from data presented in the study
el-Galley (1995)	Normal range prostate-specific antigen versus age-specific prostate-specific antigen in screening prostate adenocarcinoma	Participants were biopsy /MRI naive candidates
Elshafei (2013)	The utility of PSA velocity in prediction of prostate cancer and high grade cancer after an initially negative prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Feneley (1995)	Post-operative serial prostate-specific antigen and transrectal ultrasound for staging incidental carcinoma of the prostate	Study population already have prostate cancer
Ferro (2012)	Predicting prostate biopsy outcome: Prostate health index (phi) and prostate cancer antigen 3 (PCA3) are useful biomarkers	Participants were biopsy /MRI naive candidates
Fiamegos (2016)	Serum testosterone as a biomarker for second prostatic biopsy in men with negative first biopsy for prostatic cancer and PSA>4ng/mL, or with PIN biopsy result	Not possible to calculate a 2x2 table from data presented in the study
Filella (2014)	The influence of prostate volume in prostate health index performance in patients with total PSA lower than 10 mug/L	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Filella (2014)	Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer	Study population already have prostate cancer mixed population some participants had a dignosis of cancer
Fleshner (1997)	Prevalence and predictors of a positive repeat transrectal ultrasound guided needle biopsy of the prostate	Not possible to calculate a 2x2 table from data presented in the study

Short Title	Title	Reason for exclusion
Foo (2013)	The detection rate of prostate cancer using Prostate Specific Antigen (PSA) and Digital Rectal Examination (DRE) in Sabah	Unable to source article
Freedland (2003)	Comparison of preoperative prostate specific antigen density and prostate specific antigen for predicting recurrence after radical prostatectomy: results from the search data base	Study population already have prostate cancer
Friedl (2017)	Prostate-specific Antigen Parameters and Prostate Health Index Enhance Prostate Cancer Prediction With the In-bore 3-T Magnetic Resonance Imaging-guided Transrectal Targeted Prostate Biopsy After Negative 12-Core Biopsy	Study does not contain any relevant index tests In bore MRI
Fujita (2011)	Prostatic inflammation detected in initial biopsy specimens and urinary Pyuria are predictors of negative repeat prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Futterer (2015)	Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature	Systematic Review - relevant articles already included in this review
Galasso (2010)	PCA3: A new tool to diagnose prostate cancer (PCa) and a guidance in biopsy decisions. Preliminary report of the UrOP study	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Ganie (2013)	Endorectal coil MRI and MR-spectroscopic imaging in patients with elevated serum prostate specific antigen with negative trus transrectal ultrasound guided biopsy	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Gann (2010)	Risk factors for prostate cancer detection after a negative biopsy: A novel multivariable longitudinal approach	Not possible to calculate a 2x2 table from data presented in the study
Garcia-Cruz (2012)	Low testosterone level predicts prostate cancer in re-biopsy in patients with high grade prostatic intraepithelial neoplasia	Study does not contain any relevant index tests
Gerstenbluth (2002)	The accuracy of the increased prostate specific antigen level (greater than or equal to 20 ng./ml.) in predicting prostate cancer: is biopsy always required?	only a subset of study population ended up having a repeat biopsy, and of these 2x2 tables could not be calculated
Giulianelli (2011)	Saturation biopsy technique increase the capacity to diagnose adenocarcinoma of prostate in	Study does not contain any relevant index

Short Title	Title	Reason for exclusion
	patients with PSA < 10 ng/ml, after a first negative biopsy	tests
Gnanaprag asam (2016)	The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant prostate cancers in a repeat biopsy population	Study population already have prostate cancer Some participants had a previous diagnosis of prostate cancer
Goode (2013)	Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients	Not possible to calculate a 2x2 table from data presented in the study
Goto (2015)	Budget Impact Model for the Use of PCA3 Urine Testing in Prostate Cancer Screening	Health economics paper
Gregorio (2007)	Comparison between PSA density, free PSA percentage and PSA density in the transition zone in the detection of prostate cancer in patients with serum PSA between 4 and 10 ng/mL	Reference standard in study does not match that specified in protocol
Grey (2015)	Diagnostic accuracy of magnetic resonance imaging (MRI) prostate imaging reporting and data system (PI-RADS) scoring in a transperineal prostate biopsy setting	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification and also people on active surveillance
Guazzoni (2011)	Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting	Participants were biopsy /MRI naive candidates
Habchi (2014)	Value of prostate multiparametric magnetic resonance imaging for predicting biopsy results in first or repeat biopsy	Not possible to calculate a 2x2 table from data presented in the study
Haffner (2011)	Role of magnetic resonance imaging before initial biopsy: Comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection	Biopsy naive participants
Hambrock (2010)	Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen	Not possible to calculate a 2x2 table from data presented in the study
Hansen (2016)	Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy	Duplicate reference

Short Title	Title	Reason for exclusion
Hansen (2017)	Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy	Not possible to calculate a 2x2 table from data presented in the study
Hara (2006)	Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations	Participants were biopsy /MRI naive candidates
Haroun (2011)	Utility of free prostate specific antigen serum level and its related parameters in the diagnosis of prostate cancer	Participants were biopsy /MRI naive candidates
Hayek (1999)	The necessity of a second prostate biopsy cannot be predicted by PSA or PSA derivatives (density or free:total ratio) in men with prior negative prostatic biopsies	only a subset of study population ended up having a repeat biopsy, and of these 2x2 tables could not be calculated
Heldwein (2011)	Antibiotics and observation have a similar impact on asymptomatic patients with a raised PSA	Reference standard in study does not match that specified in protocol
Henderson (2010)	The role of PCA3 testing in patients with a raised prostate-specific antigen level after Greenlight photoselective vaporization of the prostate	Biopsy naive participants
Hessels (2009)	The use of PCA3 in the diagnosis of prostate cancer	Review article but not a systematic review
Heyns (2001)	Serum prostate-specific antigen as surrogate for the histological diagnosis of prostate cancer	Unable to source article
Hoeks (2012)	Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Hoffmann (2017)	Diagnostic Performance of Multiparametric Magnetic Resonance Imaging and Fusion Targeted Biopsy to Detect Significant Prostate Cancer	Not possible to calculate a 2x2 table from data presented in the study
Hong (2004)	Impact of prior biopsy scheme on pathologic features of cancers detected on repeat biopsies	Not possible to calculate a 2x2 table from data presented in the study
Horninger (1998)	Improvement of specificity in PSA-based screening by using PSA-transition zone density and percent	Participants were biopsy /MRI naive candidates

Short Title	Title	Reason for exclusion
	free PSA in addition to total PSA levels	
Igerc (2008)	The value of 18F-choline PET/CT in patients with elevated PSA-level and negative prostate needle biopsy for localisation of prostate cancer	Study does not contain any relevant index tests
Irani (2005)	Urinary/serum prostate-specific antigen ratio: comparison with free/total serum prostate-specific antigen ratio in improving prostate cancer detection	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Ishioka (2017)	Computer-aided diagnosis of prostate cancer using a deep neural networks algorithm in prebiopsy multiparametric magnetic resonance imaging	Conference abstract
Issa (2006)	The value of digital rectal examination as a predictor of prostate cancer diagnosis among United States Veterans referred for prostate biopsy	Participants were biopsy /MRI naive candidates
Itatani (2014)	Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies	Not possible to calculate a 2x2 table from data presented in the study
Ito (2002)	The diagnostic accuracy of the age-adjusted and prostate volume-adjusted biopsy method in males with prostate specific antigen levels of 4.1-10.0 ng/mL	Participants were biopsy /MRI naive candidates
Jang (2015)	Repeat targeted prostate biopsy under guidance of multiparametric MRI-correlated real-time contrast-enhanced ultrasound for patients with previous negative biopsy and elevated prostate-specific antigen: A prospective study	Reference standard in study does not match that specified in protocol
Janjua (2002)	The predictive value of percent free PSA using a Chiron assay in patients with a PSA of 4-10 ng/ml and a previous negative prostatic biopsy	Not possible to calculate a 2x2 table from data presented in the study
Javali (2014)	Magnetic resonance spectroscopy imaging-directed transrectal ultrasound biopsy increases prostate cancer detection in men with prostate-specific antigen between 4-10 ng/mL and normal digital rectal examination	Biopsy naive participants
Jeong (2008)	Percent Free Prostate Specific Antigen Does Not Enhance the Specificity of Total Prostate Specific Antigen for the Detection of Prostate Cancer in Korean Men 50 to 65	Participants were biopsy /MRI naive candidates

Short Title	Title	Reason for exclusion
	Years Old: A Prospective Multicenter Study	
Jimenez (2017)	Role of 18F-Choline PET/CT in guiding biopsy in patients with risen PSA levels and previous negative biopsy for prostate cancer	Study does not contain any relevant index tests
Jimenez (2017)	Role of 18F-Choline PET/CT in guiding biopsy in patients with risen PSA levels and previous negative biopsy for prostate cancer	Study does not contain any relevant index tests
Johnston (2016)	INNOVATE: A prospective cohort study combining serum and urinary biomarkers with novel diffusion-weighted magnetic resonance imaging for the prediction and characterization of prostate cancer	Study does not contain any relevant index tests Reference standard in study does not match that specified in protocol Participants were biopsy /MRI naive candidates
Jue (2017)	Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Karademir (2013)	Prostate volumes derived from MRI and volume-adjusted serum prostate-specific antigen: Correlation with Gleason score of prostate cancer	Participants were biopsy /MRI naive candidates
Kato (2016)	Analysis of repeated 24-core saturation prostate biopsy: Inverse association between asymptomatic histological inflammation and prostate cancer detection	Study does not contain any relevant index tests
Kaufmann (2015)	Direct comparison of targeted MRI-guided biopsy with systematic transrectal ultrasound-guided biopsy in patients with previous negative prostate biopsies	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Keetch (1994)	Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values	Not possible to calculate a 2x2 table from data presented in the study
Keetch (1995)	Prostatic transition zone biopsies in men with previous negative biopsies and persistently elevated serum prostate specific antigen values	Not possible to calculate a 2x2 table from data presented in the study
Kefi (2005)	Predictive value of the international prostate symptom score for positive prostate needle biopsy in the low-intermediate prostate-specific antigen range	Participants were biopsy /MRI naive candidates

Short Title	Title	Reason for exclusion
Kesch (2017)	Multicentre comparison of target and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy	Conference abstract
Khan (2003)	Can prostate specific antigen derivatives and pathological parameters predict significant change in expectant management criteria for prostate cancer?	Study population already have prostate cancer
Khang (2012)	Differences in postoperative pathological outcomes between prostate cancers diagnosed at initial and repeat biopsy	Not possible to calculate a 2x2 table from data presented in the study
Kim (2012)	The Prostate Cancer Detection Rate on the Second Prostate Biopsy according to Prostate-Specific Antigen Trend	Not possible to calculate a 2x2 table from data presented in the study
Kim (2014)	Association between obesity, prostate-specific antigen level and prostate-specific antigen density in men with a negative prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Kitagawa (2015)	Simple Risk Stratification to Detect Prostate Cancer with High Gleason Score in Repeat Biopsies in a Population Screening Follow-up Study	Not possible to calculate a 2x2 table from data presented in the study
Koca (2011)	Significance of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia in prostate biopsy	Study does not contain any relevant index tests
Kosarek (2018)	Initial series of magnetic resonance imaging (MRI)-fusion targeted prostate biopsy using the first transperineal targeted platform available in the USA	Participants were biopsy /MRI naive candidates
Kravchick (2009)	7 to 10 years' follow-up of 573 patients with elevated prostate-specific antigen (>4 ng/mL) or/and suspected rectal examination: biopsies protocol and follow-up guides	Study does not contain any relevant index tests
Kroenig (2016)	Diagnostic Accuracy of Robot-Guided, Software Based Transperineal MRI/TRUS Fusion Biopsy of the Prostate in a High Risk Population of Previously Biopsy Negative Men	Study does not contain any relevant index tests
Kubota (2008)	The potential role of prebiopsy magnetic resonance imaging combined with prostate-specific	Participants were biopsy /MRI naive candidates

Short Title	Title	Reason for exclusion
	antigen density in the detection of prostate cancer	
Kumar (2009)	Correction of prostate-specific antigen velocity for variation may improve prediction of cancer following prostate repeat biopsy	Not possible to calculate a 2x2 table from data presented in the study
Lai (2016)	Cognitive MRI-TRUS fusion-targeted prostate biopsy according to PI-RADS classification in patients with prior negative systematic biopsy results	Not possible to calculate a 2x2 table from data presented in the study
Langer (1996)	Strategy for repeat biopsy of patients with prostatic intraepithelial neoplasia detected by prostate needle biopsy	Study does not contain any relevant index tests
Lawrentschuk (2009)	The role of magnetic resonance imaging in targeting prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels	Not a peer-reviewed publication
Lazzeri (2013)	Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: A multicentric european study	Participants were biopsy /MRI naive candidates
Lazzeri (2016)	Clinical performance of prostate health index in men with tPSA>10ng/ml: Results from a multicentric European study	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Lee (1992)	Predicted prostate specific antigen results using transrectal ultrasound gland volume. Differentiation of benign prostatic hyperplasia and prostate cancer	Participants were biopsy /MRI naive candidates
Lee (2011)	Using a saturation biopsy scheme increases cancer detection during repeat biopsy in men with high-grade prostatic intra-epithelial neoplasia	Study does not contain any relevant index tests
Lee (2011)	Percentage of free prostate-specific antigen: implications in modern extended scheme prostate biopsy	Participants were biopsy /MRI naive candidates
Lee (2011)	Utility of percent free prostate-specific antigen in repeat prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Lee (2012)	Magnetic resonance imaging targeted biopsy in men with previously negative prostate biopsy results	Not possible to calculate a 2x2 table from data presented in the study

Short Title	Title	Reason for exclusion
Lee (2016)	Visually estimated MRI targeted prostate biopsy could improve the detection of significant prostate cancer in patients with a PSA level <10 ng/mL	Biopsy naive participants
Lee (2017)	Indications for a second prostate biopsy in patients suspected with prostate cancer after an initial negative prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Letran (1998)	The effect of prostate volume on the yield of needle biopsy	Study does not contain any relevant index tests
Letran (1998)	Repeat ultrasound guided prostate needle biopsy: use of free-to-total prostate specific antigen ratio in predicting prostatic carcinoma	Study comparing 2 methods of measuring PSA Dianon and Hybritech
Li (2014)	Potential benefit of transrectal saturation prostate biopsy as an initial biopsy strategy: Decreased likelihood of finding significant cancer on future biopsy	Study does not contain any relevant index tests
Lian (2017)	Assessment of free-hand transperineal targeted prostate biopsy using multiparametric magnetic resonance imaging-transrectal ultrasound fusion in Chinese men with prior negative biopsy and elevated prostate-specific antigen	Study does not contain any relevant index tests
Liu (2014)	Role of PSA-related variables in improving positive ratio of biopsy of prostate cancer within serum PSA gray zone	Participants were biopsy /MRI naive candidates
Lopez-Corona (2003)	A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session	Not possible to calculate a 2x2 table from data presented in the study
Lu (2017)	Negative Multiparametric Magnetic Resonance Imaging of the Prostate Predicts Absence of Clinically Significant Prostate Cancer on 12-Core Template Prostate Biopsy	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Lughezzani (2014)	Multicenter European external validation of a prostate health index-based nomogram for predicting prostate cancer at extended biopsy	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Luo (2014)	The PCA3 test for guiding repeat biopsy of prostate cancer and its cut-off score: A systematic review and meta-analysis	Systematic review

Short Title	Title	Reason for exclusion
Lynn (2000)	Comparative analysis of the role of prostate specific antigen parameters in clinical practice	Participants prostate cancer/prostate biopsy history unclear/unknown
Matsui (2004)	The use of artificial neural network analysis to improve the predictive accuracy of prostate biopsy in the Japanese population	Study does not contain any relevant index tests Reference standard in study does not match that specified in protocol
McMahon (2009)	Dynamic contrast-enhanced MR imaging in the evaluation of patients with prostate cancer	Review article but not a systematic review
Mearini (2014)	Evaluation of prostate-specific antigen isoform p2PSA and its derivates, %p2PSA, prostate health index and prostate dimension-adjusted related index in the detection of prostate cancer at first biopsy: An exploratory, prospective study	Participants were biopsy /MRI naive candidates
Men (2001)	Detection of prostatic carcinoma: the role of TRUS, TRUS guided biopsy, digital rectal examination, PSA and PSA density	Participants were biopsy /MRI naive candidates
Mendhiratta (2015)	Prebiopsy MRI and MRI-ultrasound Fusion-targeted Prostate Biopsy in Men with Previous Negative Biopsies: Impact on Repeat Biopsy Strategies	Study does not contain any relevant index tests
Merdan (2015)	Assessment of long-term outcomes associated with urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion at repeat biopsy	Not possible to calculate a 2x2 table from data presented in the study
Mian (2002)	Predictors of cancer in repeat extended multisite prostate biopsy in men with previous negative extended multisite biopsy	Study does not contain any relevant index tests
Moore (2013)	Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review	Participants were biopsy /MRI naive candidates
Moreira (2012)	Association of prostate-specific antigen doubling time and cancer in men undergoing repeat prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Moreira (2014)	Baseline prostate inflammation is associated with a reduced risk of prostate cancer in men undergoing repeat prostate biopsy: Results from the REDUCE study	Not a relevant study design (diagnostic test accuracy) Randomised control trial withb half the participants recceiving medication that

Short Title	Title	Reason for exclusion
		reduces prostate specific antigen
Morgan (1996)	Prospective use of free PSA to avoid repeat prostate biopsies in men with elevated total PSA	Not possible to calculate a 2x2 table from data presented in the study
Morgan (1996)	Prospective use of free prostate-specific antigen to avoid repeat prostate biopsies in men with elevated total prostate-specific antigen	Not possible to calculate a 2x2 table from data presented in the study
Morote (1997)	Comparison of percent free prostate specific antigen and prostate specific antigen density as methods to enhance prostate specific antigen specificity in early prostate cancer detection in men with normal rectal examination and prostate specific antigen between 4.1 and 10 ng./ml	Participants were biopsy /MRI naive candidates
Moul (2007)	Age adjusted prostate specific antigen and prostate specific antigen velocity cut points in prostate cancer screening	Participants were biopsy /MRI naive candidates
Moussa (2010)	Development and validation of a nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session in the era of extended prostate sampling	Validation study
Murphy (2017)	MRI-directed cognitive fusion-guided biopsy of the anterior prostate tumors	Not possible to calculate a 2x2 table from data presented in the study
Na (2017)	Prostate health index significantly reduced unnecessary prostate biopsies in patients with PSA 2-10 ng/mL and PSA >10 ng/mL: Results from a Multicenter Study in China	Participants were biopsy /MRI naive candidates
Nafie (2014)	Transperineal template prostate biopsies in men with raised PSA despite two previous sets of negative TRUS-guided prostate biopsies	Study does not contain any relevant index tests
Naya (2002)	Can volume measurement of the prostate enhance the performance of complexed prostate-specific antigen?	Study population already have prostate cancer
Ng (2005)	Prostate cancer detection with digital rectal examination, prostate-specific antigen, transrectal ultrasonography and biopsy in clinical urological practice	Participants were biopsy /MRI naive candidates

Short Title	Title	Reason for exclusion
Nicholson (2015)	The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation	Systematic review
Noguchi (1999)	Necessity of repeat biopsies in men for suspected prostate cancer	Not possible to calculate a 2x2 table from data presented in the study
Nordstrom (2016)	A population-based study on the association between educational length, prostate-specific antigen testing and use of prostate biopsies	Reference standard in study does not match that specified in protocol Not possible to calculate a 2x2 table from data presented in the study
Novara (2010)	Detection rate and factors predictive the presence of prostate cancer in patients undergoing ultrasonography-guided transperineal saturation biopsies of the prostate	Study does not contain any relevant index tests
Nyberg (2010)	PCA3 as a diagnostic marker for prostate cancer: a validation study on a Swedish patient population	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Ochiai (2011)	Prostate cancer gene 3 urine assay for prostate cancer in Japanese men undergoing prostate biopsy	Participants were biopsy /MRI naive candidates
Ochiai (2013)	Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy	Participants were biopsy /MRI naive candidates
Ohi (2004)	Diagnostic significance of PSA density adjusted by transition zone volume in males with PSA levels between 2 and 4ng/ml	Participants were biopsy /MRI naive candidates
Okada (2000)	Correlation of histological inflammation in needle biopsy specimens with serum prostate-specific antigen levels in men with negative biopsy for prostate cancer	Not possible to calculate a 2x2 table from data presented in the study
Okegawa (2000)	Comparison of two investigative assays for the complexed prostate-specific antigen in total prostate-specific antigen between 4.1 and 10.0 ng/mL	Study does not contain any relevant index tests
Okegawa (2000)	Comparisons of the various combinations of free, complexed,	Study does not contain any relevant index

Short Title	Title	Reason for exclusion
	and total prostate-specific antigen for the detection of prostate cancer	tests
Ong (2015)	Transperineal biopsy prostate cancer detection in first biopsy and repeat biopsy after negative transrectal ultrasound-guided biopsy: The Victorian Transperineal Biopsy Collaboration experience	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Osredkar (2016)	The performance of proPSA and prostate health index tumor markers in prostate cancer diagnosis	Participants were biopsy /MRI naive candidates
Panebianco (2010)	Role of magnetic resonance spectroscopic imaging ([1H]MRSI) and dynamic contrast-enhanced MRI (DCE-MRI) in identifying prostate cancer foci in patients with negative biopsy and high levels of prostate-specific antigen (PSA)	Not a relevant study design (diagnostic test accuracy) Randomised controlled trial
Panebianco (2018)	Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next?	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Park (2003)	Predictors of prostate cancer on repeat transrectal ultrasound-guided systematic prostate biopsy	Not possible to calculate a 2x2 table from data presented in the study
Park (2014)	Clinicopathologic differences between prostate cancers detected during initial and repeat transrectal ultrasound-guided biopsy in Korea	Not possible to calculate a 2x2 table from data presented in the study
Park (2015)	Comparison of re-biopsy with preceded MRI and re-biopsy without preceded MRI in patients with previous negative biopsy and persistently high PSA	Not a relevant study design (diagnostic test accuracy) Case control design
Parsons (2004)	Complexed prostate specific antigen (PSA) reduces unnecessary prostate biopsies in the 2.6-4.0 ng/mL range of total PSA	Participants were biopsy /MRI naive candidates
Patel (2004)	Parasagittal biopsies add minimal information in repeat saturation prostate biopsy	Study does not contain any relevant index tests
Pepe (2007)	Saturation prostate needle biopsy and prostate cancer detection at initial and repeat evaluation	Study does not contain any relevant index tests
Pepe (2008)	Is quantitative histologic examination useful to predict nonorgan-confined prostate cancer when saturation biopsy is performed?	Study does not contain any relevant index tests

Short Title	Title	Reason for exclusion
Pepe (2010)	Can Sonovue targeted biopsy replace extended or saturation biopsy in prostate cancer diagnosis? Our experience at primary and repeat biopsy	Study does not contain any relevant index tests
Pepe (2010)	Prostate cancer detection after one or more negative extended needle biopsy: Results of a multicenter case-findings protocol	Study does not contain any relevant index tests
Pepe (2011)	Does an inflammatory pattern at primary biopsy suggest a lower risk for prostate cancer at repeated saturation prostate biopsy?	Study does not contain any relevant index tests
Pepe (2014)	Detection rate of anterior prostate cancer in 226 patients submitted to initial and repeat transperineal biopsy	Study does not contain any relevant index tests
Pepe (2015)	Can 3-Tesla pelvic phased-array multiparametric MRI avoid unnecessary repeat prostate biopsy in patients with PSA < 10 ng/mL?	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Pepe (2015)	Anterior prostate biopsy at initial and repeat evaluation: is it useful to detect significant prostate cancer?	Participants were biopsy /MRI naive candidates some prticipants were biopsy naive
Pepe (2017)	Multiparametric MRI Apparent Diffusion Coefficient (ADC) accuracy in diagnosing clinically significant prostate cancer	Participants were biopsy /MRI naive candidates
Philip (2006)	Importance of peripheral biopsies in maximising the detection of early prostate cancer in repeat 12-core biopsy protocols	Not a relevant study design (diagnostic test accuracy)
Philip (2009)	Prostate cancer diagnosis: should patients with prostate specific antigen >10ng/mL have stratified prostate biopsy protocols?	Participants were biopsy /MRI naive candidates
Pinsky (2007)	Repeat prostate biopsy in the prostate, lung, colorectal and ovarian cancer screening trial	Duplicate reference
Pinsky (2007)	Repeat prostate biopsy in the prostate, lung, colorectal and ovarian cancer screening trial	Mixed studies with other cancers
Ploussard (2010)	The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: Does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies?	Study does not contain any relevant index tests

Short Title	Title	Reason for exclusion
Ploussard (2013)	Risk of repeat biopsy and prostate cancer detection after an initial extended negative biopsy: Longitudinal follow-up from a prospective trial	Not possible to calculate a 2x2 table from data presented in the study
Ploussard (2014)	Does PCA3 really help urologists?	Review article but not a systematic review
Pokorny (2014)	Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies	Participants were biopsy /MRI naive candidates
Ponholzer (2011)	Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Portalez (2010)	Prospective comparison of T2w-MRI and dynamic-contrast-enhanced MRI, 3D-MR spectroscopic imaging or diffusion-weighted MRI in repeat TRUS-guided biopsies	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2 study compared different elements of MRI
Pourmand (2012)	Preventing Unnecessary Invasive Cancer-Diagnostic Tests: Changing the Cut-off Points	Participants were biopsy /MRI naive candidates
Prando (2005)	Prostatic biopsy directed with endorectal MR spectroscopic imaging findings in patients with elevated prostate specific antigen levels and prior negative biopsy findings: early experience	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Prestigiacomo (1997)	Can free and total prostate specific antigen and prostatic volume distinguish between men with negative and positive systematic ultrasound guided prostate biopsies?	Study population already have prostate cancer
Quentin (2012)	Evaluation of a structured report of functional prostate magnetic resonance imaging in patients with suspicion for prostate cancer or under active surveillance	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Rabets (2004)	Prostate cancer detection with office based saturation biopsy in a repeat biopsy population	Study does not contain any relevant index tests

Short Title	Title	Reason for exclusion
Radtke (2017)	Combined Clinical Parameters and Multiparametric Magnetic Resonance Imaging for Advanced Risk Modeling of Prostate Cancer-Patient-tailored Risk Stratification Can Reduce Unnecessary Biopsies	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Ramos (2013)	PCA3 sensitivity and specificity for prostate cancer detection in patients with abnormal PSA and/or suspicious digital rectal examination. First Latin American experience	Biopsy naive participants
Ravery (1999)	Diagnostic value of ten systematic TRUS-guided prostate biopsies	Study does not contain any relevant index tests
Reissigl (1996)	Usefulness of the ratio free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening	Biopsy naive participants
Reljic (2004)	Diagnostic value of age specific prostate specific antigen in prostate cancer patients	Participants were biopsy /MRI naive candidates
Remzi (2003)	Can total and transition zone volume of the prostate determine whether to perform a repeat biopsy?	Study does not contain any relevant index tests
Remzi (2004)	Can power doppler enhanced transrectal ultrasound guided biopsy improve prostate cancer detection on first and repeat prostate biopsy?	Study does not contain any relevant index tests
Roberts (2000)	Digital rectal examination and prostate-specific antigen abnormalities at the time of prostate biopsy and biopsy outcomes, 1980 to 1997	Biopsy naive participants
Rochester (2009)	Development and validation of risk score for predicting positive repeat prostate biopsy in patients with a previous negative biopsy in a UK population	Study does not contain any relevant index tests study is a validation study of a risk score including a number of variables including age, psa and DRE
Roehrborn (1996)	Diagnostic yield of repeated transrectal ultrasound-guided biopsies stratified by specific histopathologic diagnoses and prostate specific antigen levels	Not possible to calculate a 2x2 table from data presented in the study
Roethke (2012)	MRI-guided prostate biopsy detects clinically significant cancer: analysis of a cohort of 100 patients after previous negative TRUS biopsy	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla

Short Title	Title	Reason for exclusion
		magnetic, Bvalue of at least 800s/mm2
Roobol (2004)	No reason for immediate repeat sextant biopsy after negative initial sextant biopsy in men with PSA level of 4.0 ng/mL or greater (ERSPC, Rotterdam)	Not a relevant study design (diagnostic test accuracy) Randomised control trial
Roobol (2007)	The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC)	Reference standard in study does not match that specified in protocol
Roobol (2007)	The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC)	Duplicate reference
Roobol (2010)	Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test	Biopsy naive participants
Roobol (2010)	Performance of prostate cancer antigen 3 (PCA3) and prostate-specific antigen in prescreened men: Reproducibility and detection characteristics for prostate cancer patients with high PCA3 scores (>=100)	Not possible to calculate a 2x2 table from data presented in the study
Roobol (2010)	Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test	Duplicate reference Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Roobol (2010)	Performance of prostate cancer antigen 3 (PCA3) and prostate-specific antigen in Prescreened men: reproducibility and detection characteristics for prostate cancer patients with high PCA3 scores (? 100)	Duplicate reference
Rosenkrantz (2016)	Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR	Review article but not a systematic review
Rovner (1997)	Transurethral biopsy of the prostate for persistently elevated or increasing prostate specific antigen following multiple negative transrectal biopsies	Study does not contain any relevant index tests

Short Title	Title	Reason for exclusion
Rubens (1996)	Clinical evaluation of prostate biopsy parameters: gland volume and elevated prostate-specific antigen level	Participants were biopsy /MRI naive candidates Only 5 patients had repeat biopsy
Ruffion (2013)	PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy	Participants were biopsy /MRI naive candidates
Ryden (2007)	Prevalence of prostate cancer at different levels of serum prostate-specific antigen (PSA) and different free: Total PSA ratios in a consecutive series of men referred for prostate biopsies	Participants prostate cancer/prostate biopsy history unclear/unknown
Ryu (2010)	Predictive factors of prostate cancer at repeat biopsy in patients with an initial diagnosis of atypical small acinar proliferation of the prostate	popilation diagnosed with ASAP
Saema (2012)	PSA density and prostate cancer detection	Unable to source article
Salami (2015)	In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy?	Not possible to calculate a 2x2 table from data presented in the study
Saleem (1998)	Factors predicting cancer detection in biopsy of the prostatic fossa after radical prostatectomy	Not possible to calculate a 2x2 table from data presented in the study
Satkunasivam (2014)	Human kallikrein-2 gene and protein expression predicts prostate cancer at repeat biopsy	Study does not contain any relevant index tests
Satoh (2006)	Is interval from an initial biopsy a significant predictor of prostate cancer at repeat biopsies?	Study does not contain any relevant index tests
Scattoni (2011)	The optimal rebiopsy prostatic scheme depends on patient clinical characteristics: Results of a recursive partitioning analysis based on a 24-core systematic scheme	Study does not contain any relevant index tests
Schilling (2010)	The Prostate Cancer gene 3 assay: indications for use in clinical practice	Case series
Schimmoller (2016)	MRI-guided in-bore biopsy: Differences between prostate cancer detection and localization in primary and secondary biopsy settings	Study does not contain any relevant index tests in-bore biopsy

Short Title	Title	Reason for exclusion
Schouten (2015)	Location of Prostate Cancers Determined by Multiparametric and MRI-Guided Biopsy in Patients With Elevated Prostate-Specific Antigen Level and at Least One Negative Transrectal Ultrasound-Guided Biopsy	Reference standard in study does not match that specified in protocol
Sciarra (2010)	Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy	Not possible to calculate a 2x2 table from data presented in the study Ramdomised control trial MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Segaran (2017)	The ability of free to total prostate-specific antigen and prostate-specific antigen density to detect clinically significant prostate cancer in men undergoing transperineal template biopsy	Participants were biopsy /MRI naive candidates
Serdar (2002)	Diagnostic approach to prostate cancer using total prostate specific antigen-based parameters together	Study population already have prostate cancer
Servian (2016)	Clinical Significance of Proliferative Inflammatory Atrophy in Negative Prostatic Biopsies	Study does not contain any relevant index tests
Shappell (2009)	PCA3 urine mRNA testing for prostate carcinoma: patterns of use by community urologists and assay performance in reference laboratory setting	Not possible to calculate a 2x2 table from data presented in the study Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification
Shinohara (2014)	Management of an increasing prostate-specific antigen level after negative prostate biopsy	Review article but not a systematic review
Shoji (2015)	Manually controlled targeted prostate biopsy with real-time fusion imaging of multiparametric magnetic resonance imaging and transrectal ultrasound: An early experience	Participants were biopsy /MRI naive candidates
Siddiqui (2015)	Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer	Duplicate reference Biopsy naive participants
Siegrist (2012)	PCA3 permutation increases the prostate biopsy yield	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with no stratification

Short Title	Title	Reason for exclusion
Singh (2003)	Repeating the measurement of prostate-specific antigen in symptomatic men can avoid unnecessary prostatic biopsy	Participants were biopsy /MRI naive candidates
Singh (2008)	Patient selection determines the prostate cancer yield of dynamic contrast-enhanced magnetic resonance imaging-guided transrectal biopsies in a closed 3-Tesla scanner	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Sonn (2014)	Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen	Not possible to calculate a 2x2 table from data presented in the study
Spajic (2004)	Prostate cancer detection in repeat extended prostate biopsy in men with previous negative biopsy findings	Not possible to calculate a 2x2 table from data presented in the study
Spyropoulos (2017)	Prostate Cancer Predictive Simulation Modelling, Assessing the Risk Technique (PCP-SMART): Introduction and Initial Clinical Efficacy Evaluation Data Presentation of a Simple Novel Mathematical Simulation Modelling Method, Devised to Predict the Outcome of Prostate Biopsy on an Individual Basis	Study does not contain any relevant index tests
Stamatiou (2007)	Impact of additional sampling in the TRUS-guided biopsy for the diagnosis of prostate cancer	Study does not contain any relevant index tests
Stephan (2005)	The ratio of prostate-specific antigen (PSA) to prostate volume (PSA density) as a parameter to improve the detection of prostate carcinoma in PSA values in the range of < 4 ng/mL	Participants prostate cancer/prostate biopsy history unclear/unknown
Steuber (2005)	Association of free-prostate specific antigen subfractions and human glandular kallikrein 2 with volume of benign and malignant prostatic tissue	Not possible to calculate a 2x2 table from data presented in the study
Stroumbakis (1997)	Clinical significance of repeat sextant biopsies in prostate cancer patients	Study does not contain any relevant index tests
Su (2013)	Dichotomous estimation of prostate volume: a diagnostic study of the accuracy of the digital rectal examination	Study does not contain any relevant index tests
Tamsel (2008)	Transrectal ultrasound in detecting prostate cancer compared with	Not possible to calculate a 2x2 table from data

Short Title	Title	Reason for exclusion
	serum total prostate-specific antigen levels	presented in the study for total prostate specific antigen levels
Tan (2008)	Prostate cancers diagnosed at repeat biopsy are smaller and less likely to be high grade	Not possible to calculate a 2x2 table from data presented in the study
Tan (2017)	In-bore 3-T MR-guided transrectal targeted prostate biopsy: Prostate Imaging Reporting and Data System version 2-based diagnostic performance for detection of prostate cancer	Study does not contain any relevant index tests
Tang (2013)	Transition zone PSA density improves the prostate cancer detection rate both in PSA 4.0-10.0 and 10.1-20.0 ng/ml in Chinese men	Participants were biopsy /MRI naive candidates
Tarcan (1997)	Evaluation of prostate specific antigen density and transrectal ultrasonography-guided biopsies in 100 consecutive patients with a negative digital rectal examination and intermediate serum prostate specific antigen levels	Biopsy naive participants
Teoh (2017)	The performance characteristics of prostate-specific antigen and prostate-specific antigen density in Chinese men	Participants were biopsy /MRI naive candidates
Testa (2010)	Accuracy of MRI/MRSI-based transrectal ultrasound biopsy in peripheral and transition zones of the prostate gland in patients with prior negative biopsy	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Thompson (2006)	Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial	Not possible to calculate a 2x2 table from data presented in the study
Thompson (2007)	Prediction of prostate cancer for patients receiving finasteride: Results from the prostate cancer prevention trial	Study does not contain any relevant index tests
Thompson (2008)	The performance of prostate specific antigen for predicting prostate cancer is maintained after a prior negative prostate biopsy	Duplicate reference
Thompson (2017)	Diagnostic accuracy of multi-parametric MRI and transrectal ultrasound-guided biopsy in prostate cancer	Review article but not a systematic review
Tijani (2017)	The role of the percentage free PSA in the diagnosis of prostate cancer in Blacks: Findings in indigenous West	Biopsy naive participants

Short Title	Title	Reason for exclusion
	African men using TRUS guided biopsy	
Tombal (2013)	Clinical judgment versus biomarker prostate cancer gene 3: which is best when determining the need for repeat prostate biopsy?	Not a relevant study design (diagnostic test accuracy)
Tosoian (2017)	Prostate Health Index density improves detection of clinically significant prostate cancer	Participants were biopsy /MRI naive candidates
Tosoian (2017)	Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice	Participants were biopsy /MRI naive candidates
Truong (2018)	Multi-institutional nomogram predicting benign prostate pathology on magnetic resonance/ultrasound fusion biopsy in men with a prior negative 12-core systematic biopsy	Not possible to calculate a 2x2 table from data presented in the study
Tsao (2013)	Combining prostrate-specific antigen and Gleason score increases the diagnostic power of endorectal coil magnetic resonance imaging in prostate cancer pathological stage	Study population already have prostate cancer
Uemura (2004)	Effectiveness of percent free prostate specific antigen as a predictor of prostate cancer detection on repeat biopsy	Not a relevant study design (diagnostic test accuracy)
Ukimura (1997)	Role of PSA and its indices in determining the need for repeat prostate biopsies	The thresolds used for the index tests are not clear
Van Poppel (2012)	The relationship between Prostate CAncer gene 3 (PCA3) and prostate cancer significance	Participants were biopsy /MRI naive candidates
Vickers (2010)	Prostate specific antigen velocity does not aid prostate cancer detection in men with prior negative biopsy	Not possible to calculate a 2x2 table from data presented in the study
Vourganti (2012)	Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies	Not possible to calculate a 2x2 table from data presented in the study Unclear on how positive or negative results were classified
Walz (2006)	High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series	Study does not contain any relevant index tests
Wang (2017)	Determination of the Role of Negative Magnetic Resonance	Mixed population - biopy naive and repeat biopsy or diagnosed with prostate cancer with

Short Title	Title	Reason for exclusion
	Imaging of the Prostate in Clinical Practice: Is Biopsy Still Necessary?	no stratification As well as patien ton active surveillance
Washino (2017)	Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naive patients	Participants were biopsy /MRI naive candidates
Wei (2014)	Can urinary PCA3 supplement PSA in the early detection of prostate cancer?	Not a relevant study design (diagnostic test accuracy) Randomised control trial
Wetter (2005)	Three-dimensional 1H-magnetic resonance spectroscopy of the prostate in clinical practice: technique and results in patients with elevated prostate-specific antigen and negative or no previous prostate biopsies	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Yamamoto (2014)	Management of men with a suspicion of prostate cancer after negative initial prostate biopsy results	Not possible to calculate a 2x2 table from data presented in the study
Yeniyol (2001)	The relation of prostate biopsy results and ratio of free to total PSA in patients with a total PSA between 4-20 ng/mL	Participants were biopsy /MRI naive candidates
Yu (1998)	The usefulness of prostate-specific antigen (PSA) density in patients with intermediate serum PSA level in a country with low incidence of prostate cancer	Participants were biopsy /MRI naive candidates
Yu (2016)	Performance of the Prostate Health Index in predicting prostate biopsy outcomes among men with a negative digital rectal examination and transrectal ultrasonography	Participants were biopsy /MRI naive candidates
Yuen (2004)	Clinical, biochemical and pathological features of initial and repeat transrectal ultrasonography prostate biopsy positive patients	Participants were biopsy /MRI naive candidates
Yuen (2004)	Endorectal magnetic resonance imaging and spectroscopy for the detection of tumor foci in men with prior negative transrectal ultrasound prostate biopsy	MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffussion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2
Yun (2015)	Is histological prostate inflammation in an initial prostate biopsy a predictor of prostate cancer on repeat biopsy?	Not possible to calculate a 2x2 table from data presented in the study

Short Title	Title	Reason for exclusion
Zhang (2014)	The value of magnetic resonance imaging in the detection of prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels: a meta-analysis	Systematic Review - relevant articles already included in this review
Zhao (2014)	Developing a follow-up strategy for patients with PSA ranging from 4 to 10 ng/ml via a new model to reduce unnecessary prostate biopsies	Not a relevant study design (diagnostic test accuracy)
Zheng (2008)	The use of prostate specific antigen (PSA) density in detecting prostate cancer in Chinese men with PSA levels of 4-10 ng/mL	Participants were biopsy /MRI naive candidates

Economic studies

Short Title	Title	Reason for exclusion
Blute (2015)	Addressing the need for repeat prostate biopsy: new technology and approaches	Not economic evaluation

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Appendix J – Research recommendations

Question	What is the most suitable surveillance protocol for people who active surveillance is appropriate for, as assessed by multiparametric MRI and biopsy, when there are no clinical concerns during follow-up
Population	People on active surveillance
Intervention	Active surveillance protocol
Comparator	Other surveillance protocols
Outcomes	Prostate cancer specific mortality Prostate cancer related morbidity Clinical progression/ 'late' diagnosis of progression Quality of life Patient reported outcomes
Study design	RCT/Prospective cohort study
Potential criterion	**Explanation**
Importance to patients, service users or the population	There is a variation in how follow up protocols across the country and these have not been evaluated to understand their effectiveness. The role of both primary and secondary care is not clear.
Relevance to NICE guidance	Current guidance is based on consensus
Current evidence base	Limited evidence base
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population on active surveillance to make studies in this area feasible

Question	In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer?
Population	People with negative MRI (Likert score 1 or 2)
Index tests	Any test given within 6 months of MRI to further exclude clinically significant prostate cancer.
Reference standard	Biopsy
Outcomes	Sensitivity Specificity Positive and negative likelihood ratios QoL outcomes Adverse events
Study design	Diagnostic cross sectional studies
Potential criterion	**Explanation**

Question	In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer?
Importance to patients, service users or the population	The evidence shows that about 20% of men with a Likert score 1 or 2 on MRI may have clinically significant cancer. Since the new pathway discourages biopsy in men with negative MRI, the research will help formulate a pathway that these people may follow to identify any missed clinically significant cancer
Relevance to NICE guidance	Current guidance on the follow-up protocol for men with negative is not evidence based as this is a new population as a result as the new pathway.
Current evidence base	Limited evidence as this population is relatively new
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	A large enough number of people receive a MRI of the prostate to make this study feasible.

Question	What is the diagnostic accuracy of transperineal mapping biopsy versus transperineal non mapping biopsy in the diagnosis of clinically significant prostate cancer?
Population	People suspected of cancer (biopsy naïve or repeat biopsy)
Index test	Transperineal non mapping biopsy
References	Transperineal mapping biopsy
Outcomes	Sensitivity Specificity Positive and Negative Likelihood ratios
Study design	Diagnostic cross sectional studies
Potential criterion	**Explanation**
Importance to patients, service users or the population	The committee explained that a number of providers across the country use the transperineal route for biopsy rather than the transrectal route, however transperineal biopsy can be a mapping biopsy where a large number of samples are taken from around the prostate (currently considered the 'gold standard' diagnostic test) or a non-mapping biopsy where a smaller number of samples are taken in a more focussed way (for example guided by MRI). The diagnostic accuracy of the non-mapping method is not known. Transperineal mapping biopsy is more resource intensive than non-mand the NHS is not equipped to perform a large number of these.
Relevance to NICE guidance	This research will enable NICE guideline to be more specific about which biopsy is most appropriate in which situation.
Current evidence base	The current evidence base suggests that transperineal template biopsy is the most accurate diagnostic tool for prostate cancer. It is unknown how non-mapping transperineal biopsy compares to this.

Question	What is the diagnostic accuracy of transperineal mapping biopsy versus transperineal non mapping biopsy in the diagnosis of clinically significant prostate cancer?
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people with locally advanced prostate cancer, carrying out a trial in this area should be feasible